THE CHEMISTRY AND PHYSICS
OF
ANESTHESIA

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By

JOHN ADRIANI, M.D.

Director, Department of Anesthesiology
Charity Hospital
New Orleans, Louisiana
Professor of Surgery, School of Medicine
Tulane University
Professor of Clinical Surgery and Pharmacology
Lousiana State University
Professor of General Anesthesia, School of Dentistry
Loyola University
New Orleans, Louisiana

Dedication

ARTHUR M. WRIGHT, M.D.

Teacher, Surgeon, and Friend

During the past decade anesthesiology has developed into a science and a specialty. The center of anesthesiology at New York University and Bellevue Hospital has given impetus to the remarkable advancements in this field. Dr. Wright's foresight in establishing and his guidance in developing this center will always be remembered by those who worked with him at Bellevue.

EPILOGUE

Arthur Wright passed away in 1948, but he lived to see his vision shape into reality and to see many of the trainees of the Department of Anesthesia at Bellevue spread nationwide and assume the leadership in developing Anesthesiology and occupy positions of responsibility in the specialty.

Preface to Second Edition

THE WRITER began to assemble the material for the first edition nearly twenty years ago. At that time, the selection and the assembling of the subject matter was not the difficult task that it has been to prepare the second edition. The present day literature pertaining to the subject is voluminous. In many cases in this revision individual chapters are either resumes of a massive collection of writings on a particular subject or they are a compilation of well established fundamental principles on chemistry or physics of anesthesia. To add more than has been added not only would enlarge the book beyond the point of usefulness but would also obscure the original intent of the book which was to provide necessary basic data for those who are interested in being grounded in the basic sciences associated with the administration of anesthetics.

The original edition was titled *The Chemistry of Anesthesia*. Physics was included in the first edition but in the revision this portion of the subject matter is more detailed. The title, therefore, has been changed to *The Chemistry and Physics of Anesthesia*. The general plan, grouping of subject matter and scope of the book remains the same. Basic fundamental concepts of elementary physics and chemistry which are essential for understanding the topic being presented and which the author has found by experience that the student has forgotten or has never learned are included whenever they appear to be indicated.

The writer is indebted to Dr. Frank W. Summers formerly of the Department of Anesthesia at Charity Hospital and presently in the Department of Anesthesia at Los Angeles County Hospital for suggestions and recommendations in preparation of the manuscript.

Preface to First Edition

IN RECENT YEARS emphasis in postgraduate medical instruction has drifted towards the basic sciences concerned with the specialty pursued. Of all the fundamental sciences, chemistry has reflected itself most widely in medicine. In anesthesiology, chemistry plays a significant role.

This book is an outgrowth of a teaching outline used by the writer to present chemical data related to anesthesia to postgraduate students, residents, and fellows in anesthesiology while he was an instructor at New York University College of Medicine and assistant visiting anesthetist at Bellevue Hospital, as well as in his present position at Louisiana State University and Charity Hospital.

For the sake of convenience, this book is divided into three parts. *Part I* deals with inorganic phases of chemistry related to anesthesia. *Part II* includes the organic chemistry which is essentially the chemistry of depressant drugs. *Part III* deals with the biochemical aspects of anesthesia and is devoted to chemical changes in tissues induced by the administration of anesthetic drugs to man and animals. Some overlapping occurs because the branches of chemistry are so interrelated that when applied to a medical science, such as anesthesiology, it becomes almost impossible to make absolute demarcations between the various subdivisions.

Even though medical graduates are versed in elementary chemistry, the writer has frequently found it necessary to review briefly certain fundamentals to insure clear understanding of the subject matter. Therefore, in certain sections and in some discussions, brief reviews of fundamental facts pertaining to the particular subject have been included.

Data are assembled from pertinent medical and chemical literature. The accepted clinical applications of chemistry to anesthesiology as practiced in the United States are stressed. The laboratory procedures and tests mentioned are introduced only to present underlying principles and to demonstate the range of utility or of limitation of these principles. Techniques in most instances are purposely omitted inasmuch as they are of secondary importance for clinicians. This book is for the anesthesiologist and, therefore, subject matter that may be primarily of more special interest to chemists, pharmacologists, or research workers, may not necessarily be included.

The bibliography includes general references, and, in addition, a supplemental list of references which are the source of a new data and data not ordinarily available in textbooks or monographs. A glossary of special terms, tables, and other data is also provided.

The writer is indebted to Dr. Bert B. Hershenson, Anesthetist-in-Chief to the Boston Lying-in Hospital, Boston, Massachusetts; to Dr. D. H. Batten,

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Part III

BIOCHEMISTRY RELATED TO ANESTHESIA

THE CHEMISTRY AND PHYSICS

OF

ANESTHESIA

Introduction

I NORGANIC CHEMISTRY concerned with anesthesia is chiefly the chemistry of inorganic gases and of carbon dioxide absorption. In a discussion of gases it is difficult to dissociate chemistry from physical behavior. Consequently, the physics of gases and vapors related to practical clinical anesthesia are also included in this section.

Principles of Physics and Chemistry of Solids and Fluids Applicable to Anesthesiology

INTRODUCTION

THE ANESTHESIOLOGIST must have an understanding of the physics and chemistry of gases and vapors because they, together with devices for storing, measuring and using them, comprise a liberal share of his entire armamentarium. For this reason, fundamental physical and chemical laws concerning gases and vapors will be reviewed briefly.

MATTER AND ENERGY

Matter is anything that occupies space and has mass. In the ordinary sense matter can neither be created nor destroyed. It exists in three phases, *gases, liquids* and *solids*. Matter, in all its phases, is a granular structure composed of infinitesimally invisible units referred to as *molecules*. Molecules are divisible into smaller units known as *atoms*. When a molecule of a substance is divided it loses its identity. Atoms are the smallest units of elements. All substances are composed of one or more elements. Under ordinary circumstances an element may be defined as a substance which cannot be further subdivided. Until recent years subdivision of an atom had not been accomplished. The fact that an atom can now be subdivided is well recognized. Subdivision of an atom results in loss of identity of the element. Certain large atoms are unstable and disinte-grate into smaller atoms of other elements. Energy is released in the process. Radium disintegrates into lead and helium, during which process there is a release of energy. This transmutation is a natural process which is not ordinarily accelerated or retarded. Artificial transmutation of elements is also possible. By the process known as *fission* large atoms may be subdivided into atoms of lesser mass. Energy (atomic energy) is released in the process. Atoms of small mass may be made to combine to create elements of greater mass. This process is known as *fusion.* Hydrogen atoms may be made to combine to form helium. Energy is released in the process also.

ENERGY

Matter is always associated with energy. *Energy* is the ability to do work. Like matter, energy can neither be created nor destroyed, if one speaks in the ordinary sense. However, mass and energy are two forms of the identical thing. One can be converted into the other by complex physical processes. The sum of mass plus energy remains constant. Energy can be released from matter, as was postulated by Einstein, and has been demonstrated by the nuclear physicists. A small mass can be converted into a considerable amount of energy, as can be seen by Einstein's equation $E = m\ c^2$ in

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which E equals energy and m equals mass. The constant c^2 is equivalent to the speed of light. A relatively small mass of matter is converted into a large amount of energy by fusion or fission. Fusion and fission are so difficult to accomplish that one may retain the concept that neither matter nor energy can be created nor destroyed when speaking in the ordinary sense. Energy exists in various forms. Energy is described as being *potential* when it is associated with space and *kinetic* when associated with motion. Light, heat, electricity and magnetism are forms of energy which can be transformed into kinetic or potential energy depending on circumstances.

Atomic and Molecular Weights

The atoms of an element possess an average mass which corresponds to and is known as the *atomic weight* of the element. In the case of oxygen the value 16 is assigned to the mass. The value assigned to the average mass of other elements is relative to the mass of the oxygen atom. In the case of hydrogen it is 1.008, in the case of nitrogen 14, and so on. The mass of a molecule is equal to the sum of the atomic weights of the atoms composing the molecule. The figure assigned to the mass of a molecule is referred to as the *molecular weight* of that substance. The masses of molecules of various substances also are compared to the mass of the oxygen atom as the standard.

Atomic Structure

In recent years much information has been added to the concepts of atomic structure. An atom consists of a minute nucleus composed of *protons* and *neutrons* about which revolve electrons arranged in a planetary fashion. The nucleus is positively charged since it contains positrons. *The positron is a unit of positive electricity. The electron is a unit of negative electricity.* The electron is very light compared to the proton having a mass of 1/1845 of the mass of the hydrogen atom. The proton has a mass equivalent to the numerical value of 1.0 on the atomic scale or 1/16 of the weight of the oxygen atom. A neutron is a particle of unit mass also having approximately the same weight as a proton but no electrical charge. In other words, it has no positron. The proton is considered by some to be a neutron plus a positron. Electrons are arranged in concentric rings or orbits around the nucleus. These rings, which are referred to as energy levels, are at a great distance from the nucleus, comparatively speaking. The ring closest to the nucleus is labeled the K shell, the next the L, the next the M and so on. The number of protons in the nucleus is known as the *atomic number*. The number of positive charges, or positrons, in the nucleus equals the negative charges in the orbit of electrons. The greater the number of protons in the nucleus, the larger the number of electrons necessary to achieve electric neutrality and the greater the number of electron shells. Certain elements have L, M, N, O, P and Q shells or orbits. The number of electrons in an atom, therefore, equals the number of protons. Hydrogen has one proton in the nucleus and one electron in a single orbit while oxygen has eight protons and eight electrons; therefore, the atomic number of hydrogen is 1; that of oxygen is 8. The reactivity, that is the chemical properties of an element, depends upon the behavior of the electrons. In certain atoms the electrons in the outer ring or energy level, often referred to as the valence electrons, possess a certain instability. The greatest stability is ob-

served when an element has eight electrons in the outer shell. Elements so constituted are inert chemically. Among these are helium, argon, neon, xenon and krypton. These are often referred to as the *rare gases*. Each of the shells in all elements has two electrons in the innermost shell, eight or more electrons in the remaining shells except the outer one. The outer shell has less than eight in all elements, save in the case of the inert gases which are complete with eight. Helium is an exception, since it is complete with two electrons in its outer shell. Elements whose outermost orbits contain three or less electrons tend to donate these to other atoms to achieve stability. These elements are *metals*. Elements which have five, six or seven electrons in their outermost orbits tend to take on or accept electrons from other elements willing to donate them in order to achieve stability. These elements are *non-metals*. Elements having four electrons tend neither to gain or lose electrons. They are referred to as *amphoteric*. Instead of donating or accepting, they tend to share electrons with other elements. Carbon is the most important of this type.

Chemical changes occur when electrons leave the orbit of one atom and are accepted into the orbit of another. The two atoms then are associated with each other and remain associated by this chemical bonding, often referred to as *ionic* or *electrovalent bonding*. In atoms which share electrons without accepting or donating them, the bonding is referred to as *covalent*. Covalent bonding may be polar or non-polar. If electrons are equidistant between the atoms constituting the molecule it is called *non-polar*. If the shared electrons are closer to one atom than the other, so that part of one molecule is negative with respect to the other, the molecule is referred to as *polar*. Atoms which are capable of acquiring or donating a single electron, or are able to share a pair of electrons, are said to be *univalent*. Those which acquire or donate two electrons are *bivalent*, those which acquire or share three are *trivalent*, and so on. Atoms which readily donate electrons have a *positive valence;* those which acquire them have a *negative valence*. Thus sodium has one electron in its outer orbit; chlorine has seven. When these two elements are brought together the electron of sodium passes to the orbit of the chlorine. The octet is completed and sodium chloride forms.

ISOTOPES

Atoms whose nuclei have the same number of protons in the nucleus, that is, the same atomic number and the same number of electrons in their orbits, but whose masses are different are known as *isotopes*. The differences in atomic weights of isotopes are due to the additional neutrons in the nucleus. The isotopes of an element each possess similar chemical properties because the chemical reactivity is due to the electrons and the arrangement of electrons remains the same. However, these properties are not identical in the strictest sense. The atomic number and planetary configurations, that is the number of electrons in each isotope, are identical because the number of protons is identical. In the case of hydrogen, for example, three isotopes exist which are designated as H^1, H^2, and H^3. H^1 is composed of one proton and one electron. It is the hydrogen which is ordinarily encountered in substances which contain the element such as water, the hydrocarbons and so on. H^2 consists of one proton and one neutron in the nucleus and one electron in the orbit. It is known as *deuterium* or

heavy hydrogen. This atom has a mass of two, H^2, which has a mass of three and is known as tritium, has two neutrons and one proton in the nucleus and one electron in the orbit. Tritium is also indicated by the symbol, H^3. The figure preceding the symbol of an element indicates the number of protons; the one following it and placed above refers to the total nuclear mass. Thus, $1H^3$ indicates the atom H has one proton and a mass of 3. Oxygen, nitrogen and many other elements exist as isotopes whose atoms are indistinguishable from each other in regards to chemical properties but differ in mass. The proportions of each of the isotopes in a naturally occurring element vary from element to element but are constant for a given element. An aggregate of atoms of an element possesses an average mass which is the assigned atomic weight of the element. Chlorine, for example, is a mixture of atoms whose relative weights range from approximately 35 to 37, but the average of the weights of the isotopes composing the element, in the proportions in which it occurs in nature, is 35.46. Therefore, 35.46 is considered the atomic weight of chlorine. Many isotopes have unstable nuclei which disintegrate into smaller, more stable atoms and release energy in the form of radioactivity. Certain radioactive substances are readily identifiable and are, therefore, useful as tracers in the study of metabolic processes and the absorption and elimination of certain drugs.

MOLECULAR MOTION

ADHESION AND COHESION

Molecules are in a state of incessant agitation and motion. Molecular motion increases as energy is added to a molecular aggregate and decreases as energy is removed. Molecules exhibit a force of mutual attraction. The closer they are to each other the greater this force. The force of attraction between *like* molecules is known as *cohesion.* Molecules of solids and liquids are held together by the forces of cohesion. The force is greatest in solids, less in liquids and least in gases. The attraction between molecules of *unlike* substances is known as *adhesion.* The molecules composing particles of chalk cling to a blackboard by adhesion.

The intensity of the forces of cohesion is discernible by the state in which a substance exists. Thus hydrogen oxide exists as *ice* in the solid phase, in which the mutual attraction between the molecules is great; as *water* in the liquid phase, in which the cohesive forces are diminished, and as *steam* in the gaseous phase in which the attraction is considerably reduced. The forces of cohesion diminish as the intermolecular distance increases. This reduction in the cohesive force is accomplished by the application of energy, usually in the form of heat or some type of energy which is converted to heat.

The forces of adhesion of one substance may be greater than the forces of cohesion in another. When these two substances are placed in contact with each other the one with the lesser cohesive force clings tenaciously to the one with the greater. When water is placed in a glass vessel the vessel becomes wet because the forces of adhesion of the molecules of the glass are greater than those of cohesion of the surface molecules of water. The meniscus of water in a capillary tube, therefore, is turned upward along the side of the tube because of this (Fig. 1.1). In the case of mercury,

the meniscus is turned downward because the forces of cohesion of mercury are greater than those of adhesion of glass. Mercury does not wet glass.

COMPOSITION OF GASES

Molecules of elements in the solid state are composed of single atoms. Molecules of *elemental* liquids and gases are composed of one or more atoms. Elemental gases, such as nitrogen, oxygen and hydrogen, are usually *diatomic*, that is, they contain two atoms in their molecules. Their formulae are expressed by the symbols N_2, O_2 and H_2 respectively. Helium, however, is *monatomic* and contains only one atom (He) while ozone is triatomic (O_3) and contains three atoms. The gaseous phase of sulphur may be *tetratomic* (S_4). Molecules of substances composed of more than one element, that is, the non-elementary substances, are referred to as *polyatomic* or *heteroatomic*.

HEAT AND TEMPERATURE

Energy may be added to or removed from a molecular aggregate. A gain in energy is reflected in an increase of molecular activity; a loss in a decrease. This kind of molecular kinetic energy constitutes heat energy. *Heat, therefore, is defined as the total energy* of the random motion of a molecular aggregate. One must differentiate between temperature and heat. The addition of heat to a body increases the agitation of molecules and causes the temperature to rise. The *temperature* of a molecular aggregate, therefore, *may be defined as the average kinetic velocity* of the molecules. Should this random motion cease completely the temperature referred to as *absolute zero* will have been attained. Absolute zero is discussed further on.
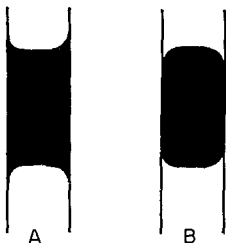
FIG. 1.1. Water drawn into a capillary tube. The meniscus (A) turns upward towards the wall of the tube because the force of adhesion of the molecules of glass is greater than the cohesive force of the water molecules. (B) The meniscus of mercury turns downward and away from the wall of the tube because the force of cohesion of the mercury molecules is greater than the force of adhesion of the glass.

EFFECTS OF MOLECULAR MOTION

When two molecules collide, energy, momentum, and mass are all conserved, since energy and matter are neither created nor destroyed. There is, however, a transferral of a certain amount of energy from one of the colliding molecules to the other. It is possible, in this manner, to transfer energy from an area where the molecules have much energy to one where there is less by a chain of collisions. A migration of molecules into space resulting from such collisions is referred to as *diffusion*. The transferral of energy from molecule to molecule explains how heat is conducted through a substance, whether it be a gas, a liquid or a solid. Momentum may be transported from groups of molecules. The manner of transport of momentum from one contiguous layer of an aggregate of molecules to the next is the study of *viscosity*. Viscosity is discussed later on.

The speed with which molecules move at any given temperature is nearly the same regardless of the nature of the substance, be it solid, liquid or a gas. The molecules of a gas travel a greater distance in a given direction when released into a vacuum than they do if released into a space containing another gas. There are fewer collisions between molecules in a given time in the former situation. All gases readily and uniformly mix with each other by the process of *diffusion*. Many liquids do likewise but at a slower rate. Solids placed into intimate contact do so also, but, obviously, in an almost imperceptible extent.

VELOCITIES OF MOLECULES

A chemically uniform gas consists of identical molecules which are in constant, chaotic and random motion. Each individual molecule has a different velocity at a given moment. An individual molecule may have one velocity when examined at one moment and a different one at another, but at a constant temperature, a constant average velocity is assignable to a group of molecules. The molecules in a gas behave like smooth elastic spheres. These spheres bounce from the stationary walls enclosing the gas, and from each other when they collide. Molecules of a gas, relatively speaking, are widely separated from each other when their intermolecular distances are compared to those of the molecules of solids and liquids.

FORCES EXERTED BY MOLECULES OF GASES

The force exerted upon the walls of a container confining a gas by the bombardment of the molecules is referred to as *pressure*. The more numerous and the more frequent the collisions with the wall, the greater the total force exerted upon the wall, and, therefore, the greater the pressure. The molecules of a gas may be brought closer together by reducing the size of the enclosure. A piston sliding into a cylindrical container forces the molecules into a smaller space as it is moved inward. This is referred to as *compression*. Expansion, the reverse effect, which occurs as the piston is moved out, causes the molecules to occupy a greater space. In a highly rarefied gas, that is one which is at a low pressure and high temperature, the molecules are relatively few and far apart. They bounce from wall to wall of an enclosing space and collide with each other rather infrequently.

PATHS OF MOLECULES IN MOTION

Collisions between individual molecules of a gas are infrequent because they are extremely small in diameter and the distance between them is relatively great. The movement of molecules, as they collide, is in a zig-zag path. The length of a path traversed by a molecule between two collisions varies from molecule to molecule and from impact to impact. There is, however, an average distance traversed between two collisions for a given mass at a given temperature and pressure. This average distance traversed between two collisions is referred to as the *mean free path*. The radius of a molecule compared to the distance of the mean free path is so small that it is negligible. The duration of a collision between two molecules likewise is negligible if a comparison is made between the time interval necessary to traverse the distance between the two collisions and the duration of impact. The molecules of a highly

rarefied gas do not attract each other except during the brief period of encounter during a collision. In other words, the forces of cohesion are nonexistent or infinitesimal in a highly rarefied gas.

In a liquid the mean free path is much shorter than in a gas. The molecules are not free to move about at random as they are in a gas, due to the forces of cohesion. The molecules in a solid, even though they are in a fixed position, oscillate in a vibratory fashion with little or no linear motion during their activity.

ADDITION OF ENERGY TO MOLECULAR AGGREGATES

When a gas is enclosed in a space whose volume may be varied by a movable piston, the molecules which strike the surface, as the piston moves inward, rebound with a higher velocity than they had before the force was applied. They, thus, acquire a higher kinetic energy from the force exerted on the piston. As they gain kinetic energy they collide more frequently and with higher energy with other molecules, and, cause them, likewise, to rebound with a higher velocity and a higher kinetic energy. The kinetic energy gained by the molecules striking the piston, therefore, is distributed among other molecules in the aggregate. The total kinetic energy of all the molecules in the enclosed space, therefore, is raised. This gain in velocity and in kinetic energy is manifested by an increase in temperature. The distribution of the kinetic energy imparted by the piston, first to the contiguous molecules, and thence through the entire molecular aggregate, explains how kinetic energy is transformed to heat and how heat is conducted through a substance. The reverse occurs when the pis-

ton is pushed out by an expanding gas. The expanding gas does work. The energy is imparted to the piston, the velocity of the molecules is decreased and the temperature falls.

GAS LAWS

Law of Pressures (Boyle's Law)

When a certain number of molecules of a gas which are occupying a unit volume, say for example one liter, are forced into an enclosure one-half this unit volume without changing the average velocity, that is, without changing the temperature, twice as many molecules strike the walls of the confining space as originally. Since pressure is due to the bombardment of the walls of an enclosure by the molecules of a gas, the pressure, therefore, is doubled. Simultaneously the volume is halved (Fig. 2.1). Forcing these same molecules into one-fourth the space causes four times as many bombardments upon the walls of the space. The pressure, therefore, is increased four times while the volume is reduced to one-fourth the original. On the other hand, if the volume is increased from one liter to two liters, half as many molecules occupy a unit space and the bombardments of the walls of the space are half as frequent. The pressure, therefore, is one-half the original when the volume is doubled (Fig. 3.1). This, of course, holds true only if the temperature is not permitted to change. These observations on relationships of volumes to pressures were formulated into a law by Robert Boyle, the English physicist in 1662. Boyle stated that the *volume of a gas varies inversely as the pressure provided the temperature remains constant*. The law further states that the pressure of a gas (P) multiplied by its
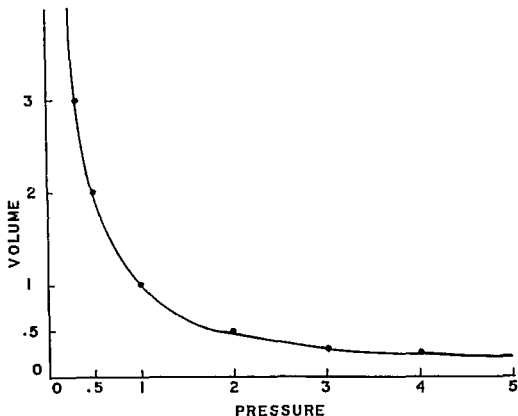
FIG. 2.1. The relationships between the volume and pressure of an ideal gas, if plotted graphically, result in a hyperbolic curve. The temperature remains constant.
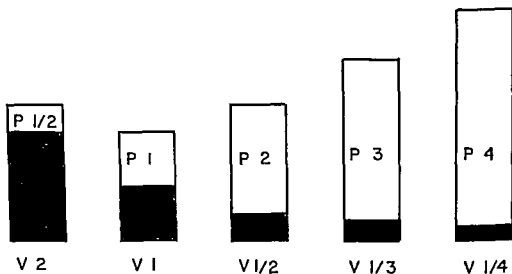

FIG 3.1. Boyle's Law. The volume of an ideal gas varies inversely as the pressure if the temperature remains constant.

volume (V) always equals a constant (K) for a fixed weight of a gas. Using symbols the law may be expressed as follows: $P \times V = K$.

REAL GASES AND IDEAL GASES

As molecules of a chemically uniform gas are brought closer to each other a mutual attraction occurs which has already been described as the force of cohesion. It is assumed that in a highly rarefied gas, that is, one in which the molecules are extremely far apart, there is no attraction between the molecules. A gas assumed to exist under conditions in which there is no attraction between the molecules is referred to as an *ideal gas*. Actually, ideal gases do not exist. The forces of cohesion in rarefied gases are so small that they are difficult to measure and are considered negligible. Boyle's Law is derived for the so-called ideal gases. At low temperatures and high pressures the forces of cohesion become significant and allowances must be made for them in computations. Gases which exist under conditions in which the forces of cohesion are of significance are known as *real gases*. Real gases behave like ideal gases at low pressures and high temperatures because, under these circumstances, the intermolecular distances are so great that the forces of cohesion become negligible. Van der Waals has modified Boyle's Law so that the effects of cohesion are taken into consideration. van der Waals' modification of Boyle's Law is discussed further on.

METHODS OF INDICATING PRESSURES

As mentioned heretofore, pressure represents the force the molecules exert on a surface. The magnitude of this force may be measured and expressed in a number of ways. One may indicate the force in terms of the height to which a gas sustains a column of liquid, such as mercury or water, in an evacuated tube. This height is expressed in units of length, usually centimeters or *inches of water or mercury*. One may indicate pressure in terms of weight per unit area. *Pounds per square inch* or *grams per square centimeter* are the usual methods of expression.

Atmospheric Pressure

The molecules of the gases composing the atmosphere exert a pressure on all earthly surfaces. In addition, the atmosphere has weight. The molecules close to the surface of the earth are compressed by those above them. In small volumes of gases the compression due to the weight of the molecules is negligible and is ignored. The force which is the sum of the pressure and the weight of the molecules of the gases in the atmosphere is great enough to sustain a column of mercury to a height of 76 cm., or a column of water to a height of 32 feet in an evacuated vertical tube. One atmosphere of pressure, therefore, is referred to as a pressure of 76 cm. or 29.9 inches mercury. If this force is expressed in weight per unit area, one atmosphere equals 14.7 pounds per square inch or 1033 gm. per sq. cm. One normal atmosphere of pressure, then, is equivalent to any of the four foregoing values.

Tension

In clinical anesthesia pressures of great magnitude are expressed in pounds per square inch or in atmospheres. Ten atmospheres, for example, is equivalent to 10×14.7 or 147.0 pounds per square inch. Gas pressures, particularly in physiology and pharmacology, are frequently referred to as *tensions*. They are expressed in centimeters of water or milli-

meters of mercury because of their small magnitude. In clinical studies pressures of magnitudes less than those of the atmosphere are referred to as *negative* pressures; those which are greater than atmospheric pressure as *positive* pressures.

VAN DER WAALS' MODIFICATION OF BOYLE'S LAW

Since Boyle's Law is applicable to ideal gases, it disregards two important factors: (1) the mutual attractions of the molecules (forces of cohesion) and (2) the volume occupied by the molecules of the gas. Boyle's Law, therefore, is not applicable to real gases, that is, to gases at low temperatures and high pressures. A modification of Boyle's Law applicable to real gases was proposed by Van der Waals. The equation he proposed has a wider range of utility than Boyle's. Boyle's expression, pressure (P) times the volume (V) equals a constant, has been modified to read as follows: The pressure (P) to which is added the reduction in pressure due to the forces of cohesion (a/V^2) times the volume (V) from which is subtracted the volume occupied by the molecules of the gas (b) equals a constant. The volume of the molecules is represented by the letter b in the equation. The volume b cannot be reduced below a certain value regardless of the pressure because, if the pressure is applied to the point of liquefaction of the gas, the resulting liquid is incompressible. The quantity "b," then, is a constant which varies with the amount and the nature of the gas. The mutual attraction of the molecules tends to slow their motion as they approach the walls of the containing vessel. This force of mutual attraction, represented by the symbol "a" in the equation, therefore, tends to reduce the pressure. Owing to the in-

ward pull of the molecules, any applied pressure "P" which is compressing a gas appears increased. This inward pull, therefore, is added to the pressure. It has been shown experimentally and proved mathematically that the reduction in pressure (a) is inversely proportional to the square of the volume of the gas. Its value in Van der Waals' expression is represented by (a/V^2). Van der Waals' modification of Boyle's Law, then, is expressed as follows: $(V - b) \times (P + a/V^2) = K$. This mutual attraction of molecules comes about by electrical forces. Like charges tend to repel and unlike charges tend to attract each other. The electrons of one molecule tend to repel those of another. Protons do likewise. The electrons of one molecule become attracted to the protons of another and tend to draw the molecules together. These forces are often referred to as Van der Waals' forces. In small molecules these forces are feeble because the electrons successfully repel each other. Light molecules, therefore, are gaseous. In molecules composed of atoms with many protons and electrons these forces operate more effectively. These substances, therefore, are liquids or solids. The addition of energy to a molecular aggregate increases the intermolecular distance and overcomes these forces and converts a solid into a liquid. The heat necessary to vaporize a substance represents the energy necessary to overcome Van der Waals' forces. Van der Waals' forces are important because they serve to explain binding of inert anesthetics to cell surfaces (Chap. 10).

Effects of Temperature on Volumes and Pressure: Charles' and Gay Lussac's Laws

Heating a gas increases molecular motion, and the gas expands and occupies

more space. Charles observed that this expansion is proportional to the rise in temperature if the pressure remains constant. Conversely, when a gas is cooled a shrinkage in volume and a reduction in speed of the molecules occurs which is also proportional to the temperature. A unit volume of gas at 0°C. contracts 1/273 of its volume for each degree of cooling below 0°C. With progressive cooling at a constant value, ultimately a point is reached at which molecular motion ceases. If cooling is accomplished at a constant pressure the gas has no volume. In order to obtain cessation of molecular motion, the temperature must be reduced to 273° below 0°C. or to absolute zero (0°A.). At this point, theoretically, molecules should have no pressure and no volume. Obviously, it is impossible to reduce the volume to zero since the mass of a substance cannot vanish because, matter can neither be created nor destroyed. Most gases liquefy or are converted to solids long before that point is reached. The law does not apply to the liquid and solid states of matter. Absolute zero, then, is simply an indication of the lowest temperature which can possibly be attained. The temperature has been approached within 0.005°C. In common parlance, one refers to —273°C. (—459°F.) as *absolute zero*, but, more precisely, the figure is —273.16°C. *The thermometric scale at which this point of molecular inactivity is zero degrees (—273°C.) is known as the Kelvin or Absolute scale.* Ice melts at 273°A. on this scale. When the temperature of a unit volume of gas at 0°C. is raised from 0° to 273°C., the expansion is in proportion to the temperature, that is 1/273 unit per degree or one whole unit (Fig. 4.1). The volume, therefore, is doubled if the pressure remains unchanged. Jaques Charles in 1787 formu-

lated this observation into the law which bears his name. The law states that the *volume of a gas, provided the pressure remains constant, is directly proportional to its absolute temperature* (Fig. 5.1.). Later, in 1802, Gay-Lussac noted that if the volume occupied by a given number of molecules of a gas at 0°C. remains constant, but the temperature is varied, the pressure increases by 1/273 of the pressure at which it existed at 0°C. for each degree rise above 0°C. Likewise, cooling causes a reduction of pressure by 1/273 of the pressure at 0°C. He also expressed these observations into a law which bears his name. Gay-Lussac's Law states that *if the volume of a gas remains constant the pressure varies directly with the absolute temperature.* The coefficient of cubical expansion of a gas is 1/273 or 0.003667 of a unit volume if the pressure remains constant.

Standard Conditions

In order that all pertinent data concerning a gas be available it is necessary to know its pressure, its temperature and its volume. Ordinarily in scientific work volumes of gases are expressed at 76 cms. Hg pressure and 0°C. These conditions are referred to as *standard conditions.* Sometimes the expression N.T.P. is used to indicate standard condition, which means normal temperature and pressure.

Avogadro's Law and Avogadro's Number

Avogadro reasoned that equal volumes of gases, even though they are chemically dissimilar and have different densities, at identical pressures and temperatures, have the same number of molecules. Since each gas is at the same temperature, their molecules must possess the same velocity, and, since

pressure is due to the total change in momentum of the molecules bouncing from the walls of the vessels, the number of molecules in each vessel must be the same. Avogadro, therefore, postulated the principle known as *Avogadro's Law* which states that *equal volumes of gases under the same conditions of pressure and temperature contain the same number of molecules.*

GRAM MOLECULAR WEIGHT AND VOLUME

At standard conditions one liter of oxygen weighs 1.429 grams, one liter of hydrogen weighs 0.089 grams. The molecular weight of a substance expressed in grams is referred to as the *gram molecular weight*. The term *mole* is used to indicate the same quantity. Experi-

mentally, it has been found that a gram molecular weight of a gas, say for example oxygen, that is 32 grams, measured at standard conditions occupies 22.4 liters. Inasmuch as one mole of oxygen weighs 32 grams and one liter of oxygen weighs 1.429 grams, the volume occupied by a mole of oxygen is computed by dividing 32 by 1.429. The resulting volume, 22.4 liters, is known as the gram molecular volume of oxygen. In the same manner the gram molecular volume may be computed for hydrogen if its weight per liter and its molecular weight are known. It has been determined experimentally and mathematically that, irrespective of the gas, the resulting volume, namely 22.4 liters, is the same for all gases. This volume is known as the
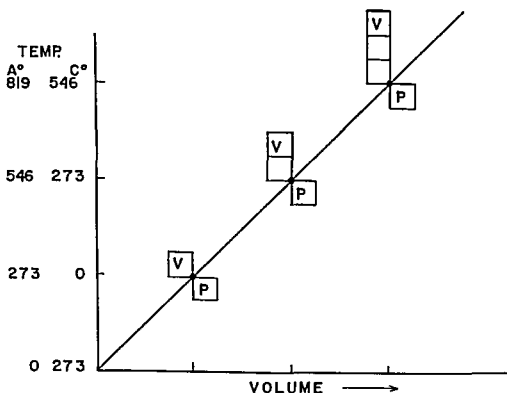

FIG. 4.1. Charles' Law. The volume of an ideal gas varies directly as the absolute temperature provided the pressure remains constant.
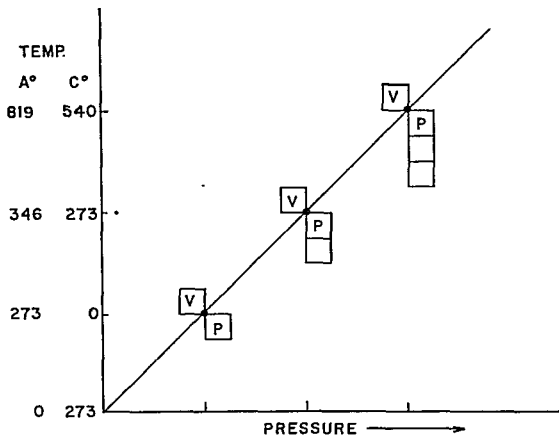
Fig. 5.1. Gay Lussac's Law. The pressure of a gas varies directly as the absolute temperature provided the volume remains constant.

molal volume or *gram molecular volume.* A gram molecular weight of a solid or liquid, if *converted into its gaseous phase* would, likewise, at standard conditions, *occupy 22.4 liters. A gram molecular* weight of ether vapor (74 grams) would occupy 22.4 liters at standard conditions. A gram molecular weight of water (18 gm.) if vaporized, and its volume expressed at standard conditions, occupies 22.4 liters. A gram molecular weight of a solid would likewise occupy 22.4 liters if it were vaporized.

A gram molecular weight, or a mole of any gas, at standard conditions, irrespective of the nature of the gas and the mass of the molecules, contains the same number of molecules and occupies the same space. This number of molecules, often called Avogadro's number, at standard conditions is 6.02×10^{23} per gram molecular weight. The number of molecules at standard conditions per cubic centimeter of an ideal gas is known *as Loschmidt's number (2.68 $\times$ 10[19] mole-cules).*

The General Gas Law

Inasmuch as pressure, volume and the number of molecules in a fixed quantity of gas are interrelated, a combination of Boyle's, Charles' and Avogadro's Laws has been formulated into what is known as the *General Gas Law.* It is expressed as follows: $PV = nRT$. P is the pressure, V the volume, n the number of molecules and R is a constant of a given numerical value which is the same for all gases which approach ideal behavior. Its numerical value depends upon the units

used for pressure, volume and temperature. Thus, for one mole of a gas at 0°C. (273°A.) at one atmosphere the volume occupied is one gram molecular volume (22.4 liters). One atmosphere $\times$ 22.4 liters = 1 mole $\times$ R $\times$ 273°A. R, therefore, equals 0.08205.

When one of the conditions of a gas changes one may compute the new pressure, temperature or volume, whichever it may be which has changed, by using the expression $PV/T = P'V'/T_1$. The pressure of the gas multiplied by the volume divided by the *absolute* temperature equals the new pressure multiplied by the new volume divided by the new temperature expressed as *absolute* temperature. If any five of the values in the equation are known the sixth may be computed.

DENSITY AND SPECIFIC GRAVITY

The weight of a given volume of a gas or a vapor may be expressed in a number of different ways. The weight of a *liter* of a gas or a vapor at standard conditions is known as its *density*. In the case of solids and liquids, density is based upon the weight of a *cubic centimeter* of the substance at 0°C. The density of a gas may be computed by dividing its molecular weight by the gram molecular volume (22.4 liters). The density is then expressed in grams per liter at 0°C. and 760 mm Hg.

In clinical practice, however, it is common to designate liquids, gases and vapors in terms of *specific gravity*. In the case of gases, specific gravity is the weight of a unit volume of the gas compared to the weight of an equivalent volume of dry air under identical conditions of temperature and pressure. The value for the weight of air is taken as unity (1). Chloroform vapor, for ex-

ample, at 20°C. is four times heavier than air. The specific gravity of chloroform, then, (air = 1) is 4. Another method of computing specific gravity is to divide the molecular weight of a gas by the molecular weight of air (28.87). The resulting value is the specific gravity expressed at 0° and 760 mm Hg (Fig. 6.1). The pressure and temperature of the gas at the time the determination was made must be indicated when expressing the weight of a gas in terms of specific gravity. In the case of solids and liquids, specific gravity is determined by comparing the weight of a unit volume of a substance with that of an equivalent volume of water and indicating the temperature at which the observation was made.

DIFFUSION OF GASES

When a gas or a vapor is liberated into a space, the molecules quickly become distributed throughout the space until they completely fill it. They exert a pressure of equal magnitude on all parts of the wall limiting the space. If two jars, one containing oxygen and another containing nitrogen, are placed mouth to mouth, the oxygen will diffuse into the nitrogen and the nitrogen into the oxygen. Both will be uniformly distributed in each of the jars within a few minutes (Fig. 7.1). This process of equalization of a molecular concentration of a gas is known as *diffusion*. The rate of diffusion depends upon the molecular weight of the substance and its temperature. The rate of diffusion, as one would expect, increases as the temperature increases. Had the jars contained not only oxygen and nitrogen, but cyclopropane and carbon dioxide respectively the same uniformity of composition would have resulted. Thorough mixing always occurs
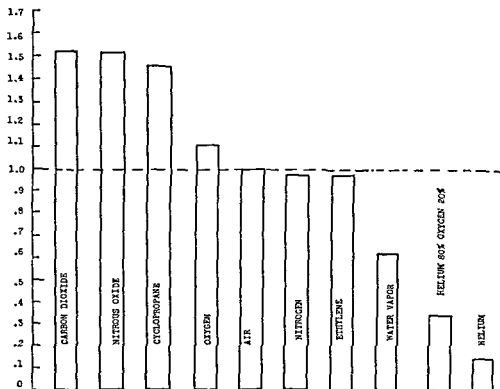
FIG. 6.1. The specific gravity of gases and vapors ordinarily used in anesthesiology. The comparison has been made with air at the same temperature and pressure (25°C.—760 mm. Hg).

so that the composition ultimately is uniform throughout. The importance of the phenomenon of diffusion in biological studies and in anesthesia is obvious. Mixing of gases would not occur were it not for diffusion. Obviously, diffusion is due to the ceaseless, chaotic motions of molecules.

Graham's Law

The rate at which the molecules of a particular gas diffuse into space depends on the mass of the molecule. The heavier the molecule, the slower it diffuses (Fig. 8.1). The manner in which gases diffuse was studied by Graham who formulated his observations into a law which bears his name. He observed that *the rate of diffusion of one gas compared to another varies inversely as the square roots of their molecular weights.*

The comparison must be made under identical circumstances and when each of the gases is at the same pressure and
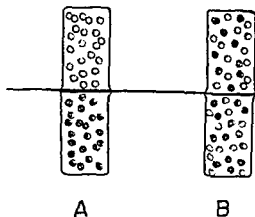

FIG. 7.1. Diffusion of gases. (A) Two jars separated by a glass slide. The upper one contains nitrogen, the lower oxygen. (B) The glass slide is removed. The molecules of each gas diffuse into the other until the concentration is uniform throughout.

temperature. Graham's Law may be illustrated by comparing the rate of diffusion of hydrogen with that of oxygen. The hydrogen molecule, whose molecular weight is 2, has 1/16 the mass of the oxygen molecule whose molecular weight is 32 (32 ÷ 2). Therefore, the relative rates of diffusion of these two gases will be $H_2/O_2 = \sqrt{16}/\sqrt{1}$ or 4:1. The hydrogen molecule, therefore, diffuses through a pore four times faster than an oxygen molecule under comparable circumstances. The law of diffusion has numerous applications in anesthesiology.

Partial Pressures (Dalton's Law)

The total pressure exerted by a mixture of gases equals the arithmetical sum of the individual pressures exerted by each of the constituents of the mixture. This observation was made by Dalton. In a mixture composed of 25% cyclopropane, (by volume) 25% oxygen and 50% nitrogen which exerts a pressure of 760 mm. Hg (one atmosphere) the pressure

exerted by the cyclopropane would be 25% of 76 or 190 mm Hg; the pressure exerted by oxygen, likewise, would be 190 mm Hg, and that of nitrogen 50% of 760 or 380 mm. Hg. The individual pressures of each gas in a mixture of gases are referred to as *partial pressures*. This expression of the behavior of a mixture of gases is referred to as Dalton's Law of partial pressures. The law is expressed by the equation $P = P_1 + P_2 + P_3$. Dalton's Law has constant application in anesthesiology.

PRESSURE GRADIENTS

A gas always diffuses from an area of higher concentration or pressure to one of a lower pressure. This differential in pressure, known as the *pressure gradient*, is an important factor in biological studies. The rate of diffusion is proportional to the difference in partial pressure (Fick's Law).

When two or more mixtures of gases of varying composition, which have

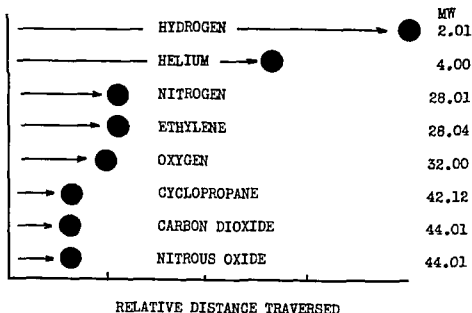|	MW
HYDROGEN	2.01
HELIUM	4.00
NITROGEN	28.01
ETHYLENE	28.04
OXYGEN	32.00
CYCLOPROPANE	42.12
CARBON DIOXIDE	44.01
NITROUS OXIDE	44.01

RELATIVE DISTANCE TRAVERSED

FIG. 8.1. Graham's Law The rate of diffusion of a gas passing through a fine opening of a porous membrane compared to another varies inversely as the square roots of their molecular weights at similar temperatures and pressures.

identical total pressures, are permitted to intermingle freely, the individual gases in the mixture diffuse from the areas of higher partial pressures to the areas of lower pressures (Fig. 9.1). Ultimately, the partial pressure of each gas will be the same throughout the entire mixture. If one of the gases is removed at a constant rate in the area of lower pressure and the supply at the area of higher pressure is inexhaustible, a constant flow of gases occurs. Such a situation exists between the gases in the atmosphere and those in the tissues. The interchange is through the medium of the blood. In the tissues, for example, carbon dioxide exerts a pressure of 80 mm. Hg, oxygen zero, nitrogen 633 mm. Hg and water vapor 47 mm. Hg. The sum total of the pressures of the gases in the tissues, including nitrogen, oxygen and water vapor is that of the atmosphere 760 mm. Hg. The carbon dioxide, whose tension in the tissues may be as high as 80 mm. Hg, diffuses into the blood where its tension is 46 mm. Hg, thence to the alveolar air where its tension if 40 mm. Hg and thence into the atmosphere where its tension is approximately zero. In this manner carbon dioxide diffuses outward from the tissues to the atmosphere. On the other hand, oxygen exerts a pressure of 152 mm. Hg in the atmosphere. In the tissues the tension is approximately zero. Therefore, the diffusion of oxygen is from the outside air to the alveoli, where the tension is 105 mm. Hg, to the blood, where it is 100 mm. Hg, and thence into the tissues (5-0 mm. Hg). The exchange, obviously, is augmented by respiratory movements. In the absence of respiratory movements, the exchange continues, but of course, it is not adequate to sustain life. The exchange which is purely physical in the absence of respiratory movements, is called *diffusion respiration*. If pure oxy-
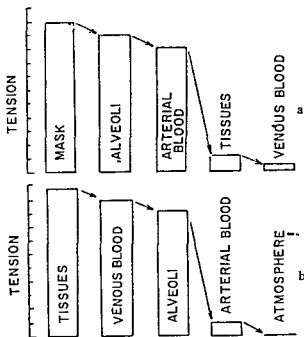
FIG. 9.1. The pressure gradient. A gas diffuses from a region of higher pressure to one of lower pressure. The carbon dioxide tension in the tissues is much greater than that in blood. (b) That in blood greater than that of alveolar air and that in the alveolar air is greater than that in atmospheric air. The gas, therefore, diffuses outward from tissues to the lips. The oxygen tension in the tissues is nearly zero. (a) In the atmosphere it is 152 mm. Hg. The pressure differential thus favors the diffusion of oxygen inward.

gen is supplied instead of air, oxygenation is improved.

FLOW RATE AND DIFFUSION

One must distinguish between the flow rate of a fluid (liquid or gas) being propelled through an orifice or a tube and diffusion through a pore. Flow rate refers to the bulk migration of molecules. Some force propels a mass of the fluid. Flow rate is dependent upon the density of the fluid. Diffusion, on the other hand, is concerned with the rate of migration of molecules. Diffusion is dependent upon the weight of the molecules of the fluid. Diffusion results from the kinetic action of the molecules. If water and alcohol

are driven through an orifice of comparable size by forces of the same magnitude, the alcohol, which is less dense (S.G. 0.78), flows faster than the water (S.G. 1.0). The flow rate is inversely proportional to the density of the fluid. Diffusion of individual molecules, however, is according to Graham's Law. Since the molecular weight of water is 18 and that of alcohol 56, molecules of water would diffuse more rapidly than those of alcohol.

Diffusion of Liquids and Solids

Diffusion is not confined solely to gases. When two miscible liquids are placed in contact with each other in the same vessel without agitation (alcohol and water, for example) their molecules diffuse in the same manner as do those of gases but at a much slower rate. Hours, days and with some liquids, even weeks may elapse before the molecules of the liquids are uniformly distributed throughout the vessel. Diffusion of molecules of one solid into another, when the two are closely in contact with each other, has been demonstrated. For practical purposes, however, diffusion of solids may be disregarded. A gas placed in contact with a liquid diffuses into the liquid. Molecules of the liquid also escape into the gas. This phenomenon will be described in more detail subsequently.

Diffusion through Membranes

One must distinguish between the diffusion due to efflux through a pore or to intermixing of several gases which are free to mingle and the diffusion through membranes. Membranes are of two types, living and inert. Diffusion through living membranes occurs in biological processes. In the living membrane factors such as the solubility of the gas in the constituents of the membrane, the thickness of the membrane, the permeability and the viscosity of the membrane play a role. The membrane is largely a film of water. The rate of diffusion is not only inversely proportional to the square root of the molecular weight of the gas but also directly proportional to the solubility of the gas in water. The passage of gases through inert membranes, such as those composed of rubber and plastic, is described in subsequent chapters.

Cooling Due to Expansion of Gases (Joule-Thomson Effect)

When a gas, particularly one which has been compressed strongly, is released into a vacuum the molecules recede from each other and lose kinetic energy because they move against the forces of mutual attraction (cohesion). Thus they lose speed. This loss of speed is manifested by a fall in temperature. Obviously, an ideal gas does not manifest this decrease in temperature as it expands into a vacuum, since there is no attraction between the molecules and loss of energy is not involved in the expansion. The decrease in temperature is noted only when real gases are allowed to expand freely. The loss of heat for air is 0.051 calories per gram per atmosphere of drop. For hydrogen it is 0.06. This phenomenon of decrease of temperature as a real gas expands freely into a space is known as the *Joule-Thomson effect*. It was named after the two physicists who first observed it. It is also referred to as the Joule-Kelvin effect. Should a compressed gas expand into a space occupied by another gas instead of into a vacuum, say for example, should oxygen under high pressure in a cylinder be released into the atmosphere, which is at a much lower pressure, an additional fall in temperature besides the one caused
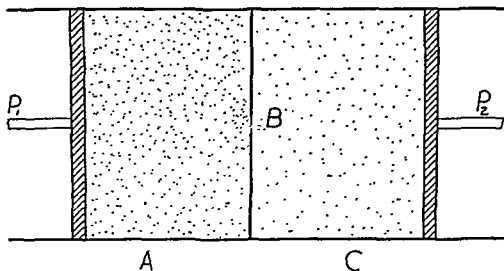
Fig. 10.1. The Joule-Thomson Effect (also known as the Joule-Kelvin Effect). *A gas under pressure* (P_1) *in chamber A escapes through the narrow orifice B to chamber C where the pressure* (P_2) *is less. A loss of velocity of the molecules passing the orifice occurs due to the fact that more particles are pulling the escaping particles backward than forward. This loss in velocity corresponds to a fall in temperature. Gases under high pressure at a low temperature show a pronounced cooling in this arrangement.*

by the expansion of the oxygen into space is observed. This additional decrease in temperature is due to the work done by the expanding gas pushing against the molecules of air which are occupying the space (Fig. 10.1).

The Joule-Thomson effect is noted when a compressed gas is released quickly from a storage cylinder into the air. The moisture in the atmosphere condenses on the cylinder valve which becomes cold as the gas passes through the orifice to the outside. Should the main cylinder valve on an oxygen cylinder be opened momentarily (cracked) to permit a blast of gas to issue from the orifice into the air a mist is noted in the path of the expanding gas. This mist is caused by condensation of the water vapor in the atmosphere adjacent to the fast moving stream of cooled gas. The Joule-Thomson principle is utilized in refrigeration and in the manufacture of a liquefiable gas, such as oxygen. In the Linde air machine compressed air (Chap. 4) is

permitted to re-expand along coils leading to the intake manifold of the air compressor. The incoming air is progressively cooled by the expanding air until it attains the temperature at which it may be liquefied by pressure.

Adiabatic Compression and Expansion (Poisson's Law)

A gas in a container which is isolated thermally from its environment becomes warmer when compressed and cools if it expands. Such volume changes of a gas which occur under conditions in which heat is neither lost to nor gained from its environment are termed *adiabatic changes.* Thus, the term adiabatic compression indicates that the compression has occurred without any transfer of energy to the environment and vice versa. Adiabatic expansion indicates no heat has been supplied from the environment. Situations in which there is no heat transfer are possible when the material composing the container is an ex-

tremely poor conductor of heat or when
pressure changes occur almost instan-
taneously. While it is theoretically pos-
sible to have no energy transfer, in actual
practice situations in which there is ab-
solutely no heat exchange do not exist.
Extremely high temperatures may de-
velop during almost instantaneous com-
pressions of even small volumes of
gases.

Situations in which adiabatic com-
pression and expansion occur are of
utmost interest to the anesthesiologist.
They are encountered particularly when
dealing with highly compressed gases.
When the main cylinder valve of a gas
at a high pressure, for example, oxygen,
is opened the gas passes into the delivery
tube between the main cylinder valve
and the diaphragm of a pressure gauge.
Almost instantaneous recompression of
the gas occurs in this space. The pres-
sure in this space, small as it is, rises from
atmospheric to approximately 2000 lbs.
per square inch in a fraction of a second.
There is no time for dissipation of the
heat resulting from this recompression
and the temperature, therefore, rises ab-
ruptly. Temperatures as high as 1000°C.
have been recorded under such circum-
stances (Fig. 11.1). Particles of dust,
grease and other combustible substances
present in the tubing may be ignited and
cause what is often termed a "flash fire."

High temperatures may be generated
when empty cylinders of relatively low
capacity are transfilled from larger cyl-
inders containing gases at high pres-
sures. The rapid recompression of the
gas in the small cylinder may cause the
temperature to rise above the ignition
temperature of combustible anesthetics.
The inadvertent mixing of oxygen at high
pressures with a combustible anesthetic
gas, such as ethylene or cyclopropane, in

incompletely evacuated cylinders may
cause fires in these cylinders. The gas
may become ignited in the cylinder at
the high temperature which develops
during recompression of the oxygen.
Rupture of the body of the cylinder may
also be possible due to the unequal ex-
pansion between its inner and outer por-
tions.

ISOTHERMAL PROCESSES

An ideal gas, that is, a gas existing at
a low pressure and high temperature rig-
idly obeys Boyle's Law. If permitted to
expand or if compressed in such a man-
ner that its temperature remains con-
stant, the pressure varies inversely as the
volume. When the pressure volume re-
lationship is plotted graphically the re-
sulting curve is a hyperbola. Such a
curve is referred to as an *isothermal* (also
isotherm). An isothermal may be plotted
for a particular gas for every possible
temperature (Fig. 12.1). There is one iso-
thermal possible for each gas at each tem-
perature, no two of which are alike. The
term isothermal indicates that the change
in volume is being accomplished without
altering the temperature. In order to
maintain a constant temperature, during
the compression or expansion, energy
must either be added or removed from
the molecular aggregate. An isothermal
process, therefore, differs from an adia-
batic process in that in the former heat
is added to the system during expansion
or removed during compression, while
in the latter there is no transfer of
energy.

Solubility of Gases (Henry's Law)

The molecules of a gas overlying the
surface of a liquid penetrate into the
liquid and intermingle with the mole-
cules of the liquid. The gas is then said

Fig. 11.1. The theoretical temperature which can be attained by the instantaneous adiabatic compression of oxygen. At pressures of 2000 lbs. per sq. in. temperatures in the order of 1000°C. (1800° F.) may be attained.
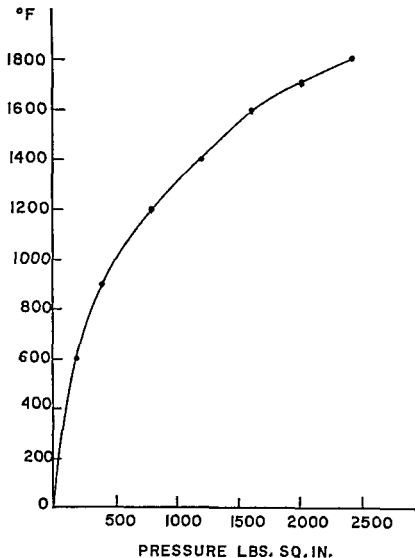
to dissolve in the liquid. Eventually, an equilibrium is established between the dissolved gas in the liquid and the undissolved portion overlying the liquid. As many molecules pass into the liquid as pass out of it to the overlying atmosphere. The molecules within the liquid exert the same pressure, often referred to as *tension*, as they exert in the gas overlying the liquid. The molecules of the solvent do not interfere with the freedom of movement of the molecules of the gas. Thus, the tensions of the gas within and without the liquid are identical. When the number of molecules, or in other words the pressure of a gas over-

lying the liquid is increased, additional molecules pass into the liquid. The tension within the liquid is increased and eventually an equilibrium is re-established between the gas in the liquid and that overlying the liquid. Should the pressure of the gas overlying the liquid be reduced, molecules of the gas escape from the liquid until the tensions over, and within the liquid, are equal and equilibrium is re-established. It is obvious, then, that the solubility of a gas in a liquid depends upon the pressure of the gas overlying the liquid (Fig. 13.1).

If the atmosphere overlying the liquid is composed of a mixture of several gases,
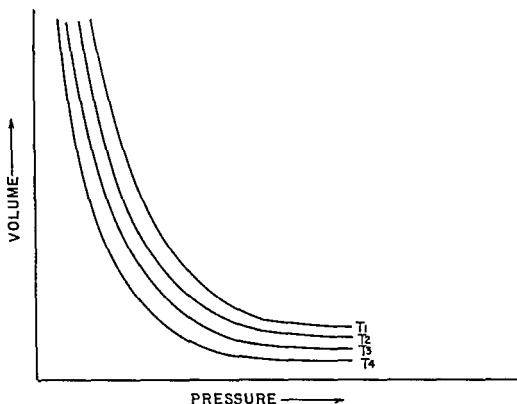
Fig. 12.1. Isothermals obtained by plotting the pressure-volume relationships of an ideal gas at various temperatures. A different isothermal exists for a particular gas at each given possible temperature.

each gas dissolves in the liquid in proportion to its partial pressure. The total pressure of the molecules in the liquid equals the total pressure of the gas overlying the liquid. Each gas dissolves in the liquid independently of the other gases and in direct proportion to its own particular partial pressure (Fig. 14.1).

These observations concerning solubility of gases in liquids were observed and formulated into a law by William Henry in 1803. The law which bears his name states that *if the temperature remains constant the quantity of a gas, that is, the total number of molecules, which dissolves in a liquid varies directly as the pressure of the gas overlying the liquid.* Thus if 10% of a gas, by volume, in an inhaled mixture causes 10 milligrams of a gas to dissolve in the plasma, 20%

causes 20 milligrams, 30% causes 30 and so on, provided, of course, that the total pressure of all the gases in the lungs remains the same.

The *volume* of a gas which dissolves in a liquid remains constant at a given temperature. The pressure-volume relationships are in accordance with Boyle's Law. Thus, it can be said that *the volume of a gas which dissolves in a liquid at a given temperature is independent of the pressure.* This may be explained by the following illustration: Assume that, under standard conditions, one cubic centimeter of a certain gas contains one million molecules and that this volume dissolves in a unit volume of a liquid. If the pressure is doubled, two million molecules dissolve in that unit volume of liquid, but at the *doubled* pressure two

Fig. 13.1. Henry's Law. The solubility of a non-reacting gas in a liquid varies directly as the pressure, provided the temperature remains constant. The volume of a gas which dissolves in a liquid is independent of the pressure, provided the temperature remains constant.
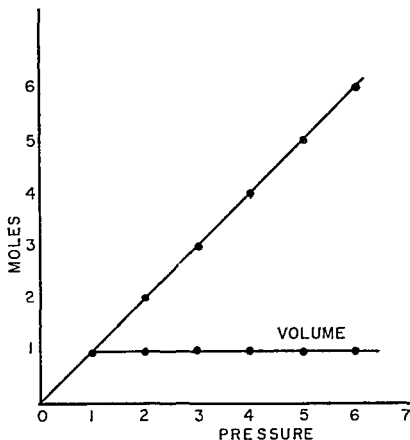
million molecules still continue to occupy the one unit volume. If the pressure is tripled three million molecules dissolve, but at three times the pressure

three million molecules still occupy the same unit volume. The volume will always be one cubic centimeter for a given gas in a given liquid at a given tempera-
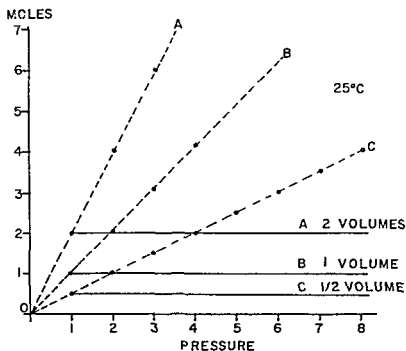

Fig. 14.1. The amount of a particular gas in a mixture of gases which dissolves in a liquid is directly proportional to the partial pressure of that gas. The amount which dissolves is independent of other gases.

ture irrespective of the pressure if the number of molecules is varied in proportion to the pressure.

The actual amount of gas which dissolves in a liquid varies with the chemical nature of the particular gas and the solvent. Henry's Law applies to gases which do not combine chemically with the solvent to form new compounds. The Law is applicable to the solution of oxygen, helium, nitrogen, nitrous oxide, ethylene, cyclopropane and other non-reactive gases in water or other liquids. Carbon dioxide combines with water to form carbonic acid. More carbon dioxide dissolves in water than can be accounted for by Henry's Law. The carbon dioxide combines with water to a limited extent, however. As soon as the solvent is saturated with carbonic acid, the remaining gas dissolves in the solvent as free carbon dioxide and obeys Henry's Law.

Gases dissolve in oils, alcohol, ether and other liquids. The solubility of a gas varies for different liquids. Nonetheless, if no interaction occurs between a solvent and a gas, Henry's Law is applicable to liquids other than water.

TENSIONS EXERTED BY GASES DISSOLVED IN A LIQUID

Water equilibrated with oxygen at 760 mm. Hg pressure and 0°C. absorbs 4.9 ml. of the gas per 100 ml. Oil equilibrated with oxygen at the same pressure and temperature absorbs much more of the gas. In either case, the tension of the gas in each solvent is the same, 760 mm. Hg. When a liquid, saturated with a gas at a given tension, is placed in contact with another liquid which is immiscible with the first, for example oil and water, a partition of the gas takes place between the two liquids.

The amount partitioned between two liquids varies with the nature of the liquids and the gas. Should this diphasic system be converted to one which is triphasic by placing the water overlaid by oil into a container so that the oil phase only comes into contact with a gas (when an equilibrium is established) the tension exerted by the molecules of the gas is the same in all three phases (Fig. 15.1). When the pressure of the gas is reduced the equilibrium is disrupted and molecules of the gaseous substance pass from the water into the oil and from the oil outward into the gaseous phase. If the pressure is increased they
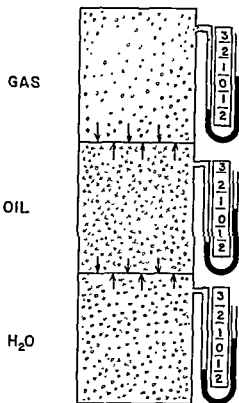

FIG. 15.1. The diagrammatic representation of the equilibrium which is attained when a gas overlies an oil phase which in turn overlies a water phase. The gas dissolved in the oil is in equilibrium with the gas dissolved in water. At equilibrium the tension exerted by the molecules of the gas is the same in all three phases.

pass into the oil and into the water until equilibrium is re-established. The passage of gases into intracellular fluids, to a certain extent, occurs in this manner.

If the gas overlying a liquid is a mixture of several gases, say for example, cyclopropane, oxygen and nitrogen, and the tension of one in the gaseous phase is reduced, say cyclopropane, the cyclopropane in the oil diffuses outwards until equilibrium is re-established. If the total pressure is kept constant, say by the addition of nitrogen to offset the decrease in tension of the cyclopropane, the nitrogen increases in concentration in the liquid phase until an equilibrium for nitrogen is re-established. Nitrogen replaces the cyclopropane in the liquid. This same principle is applicable to patients who are being anesthetized. The anesthetic gases or vapors displace nitrogen in the blood and tissues during induction and are replaced by it during recovery.

Application of Henry's Law is seen daily when gases and vapors are inhaled by patients. The partition of the gas between blood, tissue fluids and between the alveoli and blood is in accordance with Henry's Law.

ABSORPTION AND SOLUBILITY COEFFICIENTS

The volume of a gas dissolved in a unit volume of a liquid at one atmosphere pressure (760 mm. Hg) at the temperature of the experiment reduced to 0°C. and 760 mm. Hg expressed as a numerical value is called the *Bunsen absorption coefficient* for that particular gas in that given liquid. This absorption coefficient, named after Bunsen, who introduced it, is designated by the Greek letter α (alpha). The Bunsen absorption coefficient for oxygen is 0.049. Since 4.9

volumes of oxygen dissolve in 100 volumes of water 0°C. and 76 mm. Hg, 0.049 cc. dissolve in 1 cc. The International Critical Tables, and various hand books on physics and chemistry, list values for absorption coefficients of common gases dissolved in various solvents. There are several coefficients to express solubility in liquids. Another expression, the *solubility coefficient* refers to the volume of gas reduced to 0°C. and 760 mm. Hg which dissolves in one volume of the solvent at the temperature of the experiment when the partial pressure of the gas is equal to 760 mm. Hg minus the vapor pressure of the solvent. The Kuenen absorption coefficient (?) refers to the volume of gas at a partial pressure of 760 mm. Hg dissolved at the conditions of the experiment by a quantity of solution containing one gram of solvent. The Raoult absorption coefficient refers to the number of grams of gas dissolved in 100 ml. of solvent at the temperature of the experiment when the partial pressure of the gas is 760 mm. Hg.

Another expression used to designate solubility of gases in fluids is the *Ostwald solubility coefficient* indicated by the letter λ (lambda). This refers to the ratio of the volume of a gas absorbed to the volume of solvent at the temperature and pressure of the experiment. The volume and temperature are not reduced to standard conditions but remain at those of the experiment. The vapor pressure of the liquid is taken into consideration in computations. When a gas is shaken with a liquid at atmospheric pressure, the total pressure of that gas is not equal to the external or atmospheric pressure. Instead, it is the pressure equivalent to the atmospheric pressure minus the vapor pressure of the solvent. If air is shaken with water in a closed

bottle at 20°C. the pressure exerted by the air is 76 cms. Hg. From this is subtracted 1.75 cms. Hg (the vapor pressure of water). The pressure of the air is, thus, 74.25 cms. Hg instead of 76 cms. The volume of air which dissolves in a unit volume of water expressed at these conditions is the solubility coefficient at 74.25 cms. Hg at 20°C. The Ostwald solubility coefficient is used in biological and physiological studies because values for solubility of gases are expressed at the conditions of the experiment.

More important yet is the *distribution coefficient.* This is the ratio of the solubility coefficient of one gas in fluid phase A to the solubility coefficient in another fluid designated as B when an equilibrium exists between both solutions and the gas. This is also known as the *partition coefficient.* The Ostwald solubility coefficient is not the same as the distribution coefficient, even though it is often designated as such.

Effect of Temperature on Solubility of Gases

Less of a gas dissolves in a solvent as the temperature rises. The air bubbles which appear inside a vessel when water is heated are evidence of decreased solubility of air in water at the higher temperature. Anesthetic gases are less soluble in blood and water at body temperature (37.5°C.) than at room temperature (25°C.). A gas dissolves in the blood of a patient who has a high fever than in that of one who has a normal body temperature. During hypothermia more gases dissolve in blood than at normal body temperature.

Dissolved Substances and Gas Solubility

Dissolved substances such as carbohydrates, proteins, electrolytes, salts and other compounds reduce the solubility of gases in liquids. For this reason the solubility coefficients of gases in body fluids, such as lymph, plasma or blood, even though these fluids are chiefly water which contains dissolved electrolytes and organic substances, are less than they are in pure water. Exactly why dissolved substances reduce solubility is not completely understood. The depression in solubility is not strictly proportional to the concentration of the solute. It is relatively greater in dilute solutions. The solubility of a gas in aqueous solutions of various substances may not differ greatly from that in pure water if it dissolves in pure water according to Henry's Law. In a solution composed of substances besides molecules of the solvent, such as a saline solution, the solubility varies with changes in pressure in accordance with Henry's Law, provided there is no chemical union between the gas and the substances which are dissolved in the liquid.

LIQUEFACTION OF GASES

When molecules of a gas are forced closely together by compression the kinetic energy of the force pushing them together is transmitted to the molecules. The gas molecules, then, move faster. Therefore, not only do a greater number collide with the walls of the confining space, which is undergoing a reduction in volume, but they do so with greater force due to the increased velocity. The cohesive forces assume greater activity since the intermolecular distances are decreased. As more and more molecules are forced into the space, the cohesive force increases to the point that the gas liquefies. In some gases, the molecular motion is so violent that the molecules never come close enough to each other for liquefaction to occur. The gas does

not liquefy unless molecular activity is decreased by removing energy by cooling. After cooling, pressure then does cause liquefaction. A temperature exists for each gas above which liquefaction cannot occur irrespective of the magnitude of the applied pressure. This temperature is known as the *critical temperature*. The pressure necessary to cause liquefaction at the critical temperature is known as the *critical pressure*. The weight of a unit volume of a substance at the critical temperature and pressure is called the *critical density*. This is expressed as d_o. The volume occupied by a gram mole at the critical temperature and pressure expressed as milliliters per gram mole is known as the *critical volume*. This is expressed by the symbol v_o. Pressures of less magnitude than the critical pressure will not liquefy a gas irrespective of the degree of cooling. Helium must be cooled to an extremely low temperature ($-268.9°C.$) before it is liquefied by pressure. The pressure required for liquefaction at this temperature is comparatively small, however, being 2.2 atmospheres. Further cooling of a liquefied gas causes solidification. Ideal gases are more difficult to compress at high temperatures than real gases. Real gases are more compressible than ideal gases at moderate or low temperatures.

FLUIDS

NATURE OF FLUIDS

Fluids are substances which are capable of flowing. *Flow is a motion through a constraint* which is accompanied by a deformation of the fluid. Fluids are either *liquids which have no definite shape*, but have size, or they are *gases which have neither definite shape nor size*. Solids may flow if powdered, although they do so with difficulty. A liquid takes the shape of the part of the container with which it is in contact. Liquids assume the shape of the container but do not necessarily fill the space offered them. Gases spontaneously expand into a space offered them, no matter how large the space may be. This is done by the process of diffusion. Liquids are so slightly compressible, that, from a practical standpoint, they may be considered non-compressible. A relatively large compressive force applied to a liquid causes a slight or negligible diminution in volume.

FLOW OF FLUIDS THROUGH TUBES AND ORIFICES

Fluids pass through tubes and orifices. One must differentiate between a tube and an orifice because a fluid behaves in one way when it passes through a tube and in another when it passes through an orifice. *A tube may be defined as a pathway through which a fluid may pass, the diameter of which is considerably less than the length. An orifice, on the other hand, is an opening through which a fluid may pass, the diameter of which is considerably greater than the length* (Fig. 16.1). The ideal orifice has a negligible length. An efflux of a fluid occurs through an orifice when there is a pressure difference on either side of the orifice. The flow, obviously, is from the area of the higher to the one of lower pressure. The rate of flow of a gas through an orifice varies inversely as the square root of the density of the gas. Thus, hydrogen which is 1/16 as dense as oxygen flows through an orifice 4 times faster than oxygen. Fluids, likewise, flow through a tube of uniform diameter from a region of higher pressure to one of lower pressure and continue to flow until the pressure is equal at both ends. The rate of flow
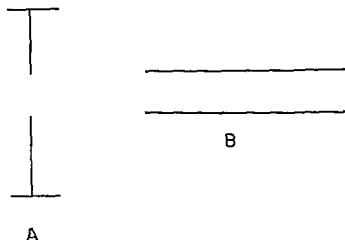
FIG. 16.1. The difference between an orifice and a tube. An ideal orifice (A) is an opening which has width but no length and which permits passage of a fluid. A tube (B) has length. The diameter of the passage is less than the length. An orifice merely has perimeter.

through a tube does not depend upon density, however. This is discussed later.

STEADY FLOW OF A FLUID

When the velocity of a fluid flowing through a tube has a fixed magnitude and a fixed direction at every point throughout the mass of the fluid, the fluid is said to have a *steady flow*. The velocity does not change at a given point with the lapse of time. The velocity may, however, be different at different points.

THE LAW OF CONTINUITY

Idealistically speaking, in a unit time the volume of an incompressible fluid which is propelled by a force through a tube of varying cross-sectional diameter, if friction is disregarded, is the same at each of the cross-sections of the tube. The velocity, however, varies with the cross-section of the tube, and is, obviously, greatest at the constricted portion of the tube. The volume flowing at each variation in cross-section is proportional to the cross-sectional area times the velocity. The ratio of the velocity at any two cross-sections is equal to the inverse ratio of the cross-sectional areas. In

other words, if the area is reduced by one-half at a certain point, the velocity is doubled at that point. The quantity of flow times the velocity, then, is a constant at all portions of the tube *provided friction is disregarded*. This constancy of flow of a fluid, without loss of energy, through a tube of varying cross-sectional area is known as the *law of continuity*.

LAMINAR AND TURBULENT FLOW

As a fluid streams through a tube at a steady flow, the molecules composing it move along in an orderly fashion in paths parallel to the walls of the tube. Such an orderly movement of molecules is referred to as a *laminar flow*. When the paths of the molecules are not parallel to the walls of the tube, but, instead, are haphazard and at angles to the walls of the tube, the flow is then described as *turbulent* (Fig. 17.1). The difference between a turbulent flow and a laminar flow is of utmost interest to the anesthesiologist. More energy is required to drive a fluid through a tube having a turbulent flow than one which has a laminar flow. Laminar flows are orderly and occur at low velocities. Turbulent flows are disorderly and are associated with high velocities. If the paths
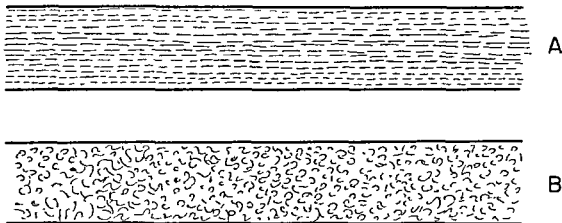
FIG. 17.1. In a laminar flow of a fluid the molecules move in an orderly fashion in paths parallel to the wall of the tube (A). When the flow is turbulent the paths of the molecules are haphazard and at various angles to the walls of the passageway (B).

taken by molecules in a laminar flow could be visualized they would appear as lines parallel to the wall of the tube. In a turbulent flow, since there is no uniformity of movement, the paths would appear irregular and disorganized. The flow of a fluid through an orifice is turbulent. The term *eddy currents* is often used to describe the disorganized paths taken by fluids. These are noted particularly in turbulent flows. The orderly paths of molecules in a laminar flow are referred to as *stream lines*. If the cross-section of a tube is varied by interposing a constriction between the two ends, the stream lines, if they could be visualized, would appear closer together in the constricted portion than they would in the wider portions (Fig. 18.1). The velocities of the molecules in the constricted por-

tion are greater than in the wider portion.

RESISTANCE TO FLOW OF FLUIDS

Realistically speaking, irrespective of whether or not a flow is laminar or turbulent, more energy is necessary to force a fluid through a tube than is accounted for by the law of continuity. This additional energy is utilized to overcome friction. A decline in pressure occurs as a fluid flows through a tube. This decline in pressure is proportional to the rate of flow, if the flow is laminar. If the flow is turbulent, the decline in pressure is much greater. In most cases it is equal to the square of the rate of flow. A *critical flow rate* exists for a given diameter of a tube for a given fluid at a given temperature. When the flow rate of a fluid in

FIG. 18.1. The streamlines in a tube of varying cross-sectional areas are closer together and move more rapidly at the constricted than at the wider areas. If the distance transversed by a molecule in a unit of time could be visualized, it would be less at the wider portion than at the constricted. The molecules would be closer together.
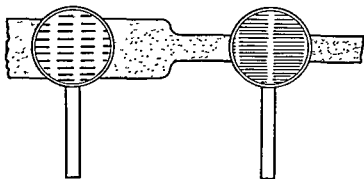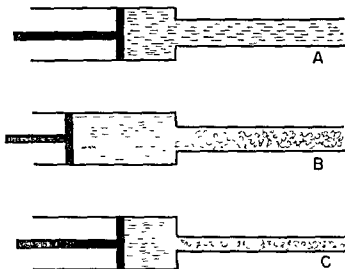
FIG. 19.1. (A) A fluid being forced through a tube with a unit of pressure exerted over a unit of time causes a laminar flow.

(B) The flow rate is doubled and exceeds the critical flow rate converting the flow from laminar to turbulent.

(C) The diameter is reduced by ½, the pressure and time are the same. The flow becomes turbulent.

a particular tube exceeds this critical flow rate, the flow is no longer laminar, but becomes turbulent (Fig. 19.1). The critical flow rate varies directly as the diameter of the tube. The narrower the tube, the less the flow rate necessary to convert a flow from a laminar to a turbulent one. The wider the tube, the greater the volume of fluid which may be discharged through it in a unit of time before a laminar flow is converted to a turbulent one.

TURBULENT FLOW AND RESISTANCE

In anesthesia practice the decline in pressure which results when a gas flows through a tube is termed *resistance*. In order to maintain the flow at a constant rate in the face of resistance additional energy must be supplied. This additional effort required to overcome the impedance to a flow of fluid is called *friction head*. Greater respiratory efforts are made to overcome resistance and to maintain an unvarying minute volume exchange. The most common cause of resistance is narrowing of the airway. The less the diameter of a tube and aperture through which a patient breathes, the

greater the effort necessary to maintain adequate gaseous exchange. The increased effort causes an increase in negative pressure in the pleural space which compensates for the added resistance and maintains an adequate ventilatory exchange. The blood oxygen and carbon dioxide tensions may be normal when resistance to respiration is present, but this may be misleading because such data do not reveal the fact that additional ventilatory effort is being made. Not only is more effort required on inspiration, but also, effort must be made during expiration to completely evacuate the lungs to overcome this resistance. Ordinarily, expiration is passive.

Changing the direction of flow by angulation of a tube, introducing valves and baffles, and the use of other devices which disrupt and scatter the stream lines may convert a flow from laminar to turbulent. When a flow which is laminar is changed from a linear one to a right angled one it becomes turbulent at the angle (Fig. 20.1). Beyond the angulation if the path continues again in a linear direction, with no change in diameter of the tube, the flow gradually reverts to a

laminar one once more. If the flow is diverted by a curved elbow instead of a right angled piece, it still becomes turbulent, but to a lesser degree. It is obvious, then, that if there is to be minimal resistance in anesthesia and inhalation therapy appliances, the apertures and tubes must be of the widest possible diameter and all tubes must be as straight as possible to permit flows to change direction gradually. Local regions of turbulence are created at constrictions, angulations and at all points in which a fluid in motion deviates from a straight line pathway.

Bernoulli's Theorem

A unit volume of a frictionless, ideal, compressible fluid moving with a steady flow through a tube has a constant total energy. When a fluid flows through a tube of varying cross-sectional diameter, the velocities of various segments of fluid, as is postulated by the law of continuity, are greatest where the diameters are least. Likewise, it follows that pressures are least at the points of greatest constriction. Manometers placed at the most constricted and widest portion of such a tube demonstrate this. The mathematical relationships of the total

energies involved in such flows have been summarized by Bernoulli in his theorem. The reader is referred to textbooks of physics for the derivation of this theorem. In essence Bernoulli's theorem states that *the pressure of a fluid flowing through a tube of varying cross-sectional diameters is least at the point of greatest constriction and the speed is greatest at this point, and that at the widest portion the pressure is greatest and that the speed is least.* There are numerous applications of this principle in anesthesiology.

At subsonic speeds compression of gases is disregarded when considering flow of fluids. Bernoulli's Theorem of interchangeability of velocity head and static head is utilized. This permits the employment of the principle of continuity. The product of the cross-sectional area of flow and the velocity is a constant at all points by a finite quantity of fluid. This is represented by the equation A (area) $\times$ V (velocity) $=$ K.

The Principle of the Venturi Tube

Under ideal circumstances, as a fluid passes through a constricted portion of a tube to an area distal to the constriction where the diameter reverts to the original value proximal to the constriction,

Fig. 20.1. Distortion of the pathway of a fluid converts the flow rate from laminar to turbulent. In a right angled distortion flow rate becomes turbulent at the angle and continues as a laminar flow when the pathway becomes linear. If the tube is curved flow still becomes turbulent but to a lesser degree.
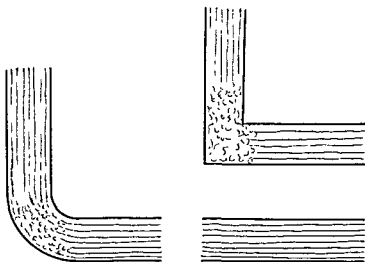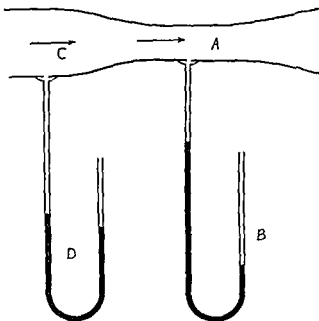
FIG. 21.1. The lateral pressure exerted by a fluid passing through a tube of varying diameter is greatest in the widest area where speed is least. Pressure is least at narrowest portion where speed is greatest. The pressure of an ideal fluid in an ideal frictionless tube reverts to the original pressure in the downstream portion of the tube beyond the constriction as the diameter is restored to its original value.

the pressure and the velocity likewise revert to the original values existing in the proximal portion (Fig. 21.1). Venturi noted that in actual practice, however, the pressure is not restored to the original value if the constriction flares out abruptly to the original diameter. However, if the tube widens out gradually from the point of constriction, in a cone like manner, at an angle not exceeding 15°, the velocity and pressure will revert to near the original values (Fig. 22.1). Venturi utilized this principle, as well as the principle enunciated by Bernoulli, in the design of a device known as the *Venturi tube.* The Venturi tube consists of a constricted tube in which calibrated

manometers are placed at the constriction and the down stream dilated portions respectively (Fig. 23.1). The Venturi tube may be used to measure the volumes and rate of flow of fluids. By noting the differences in pressure at each point it is possible to compute the quantity of fluid delivered in a unit of time through a tube.

USES OF THE VENTURI PRINCIPLE

By driving a fluid through a constricted portion of a Venturi tube at a high velocity and allowing the constriction to gradually widen out in a conical fashion, it is possible to develop a pressure at the constriction which is sub-
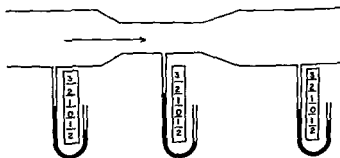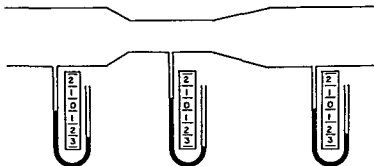

FIG. 22.1. The pressure distal to the constriction is less than in the proximal portion if the diameter reverts to the original abruptly.

atmospheric. By placing a sidearm at right angles at the point of greatest constriction, where the pressure is least and where it becomes subatmospheric, another fluid may be drawn inward and mixed with the fluid being driven through the main tube (Fig. 24.1). Such a device is known as an *injector*. A multitude of devices used in medicine embody the principle of the injector. The fluid flowing through the tube, known as the driving fluid, may be a liquid or a gas. The fluid aspirated through the sidearm, likewise, may be either a liquid or a gas. When the aspirated fluid is a liquid and the propelled fluid is a gas, the particles of liquid strike the stream of gas. The gas is at a high velocity. The liquid, therefore, is subdivided into small particles. If the particles are of a low mircon size a *mist* forms. *Atomizers* and *nebulizers* operate in this manner. Aspirators ordinarily found on resuscitators and certain models of anesthesia apparatus operate in this manner. They are driven by compressed air or from the high pressure

oxygen supply. The propelled and aspirated fluids in an injector may both be liquids, as in the water suction, or they may both be gases as they are in the mechanism which causes the negative pressure phase of mechanical resuscitating units of the "blow and suck" type. The *injector* on the oxygen therapy meter masks allows air to be drawn into the meter and mixed with oxygen. This device is also based on the Venturi principle (Figs. 25.1, 26.1).

The ratio of aspirated fluid to propelled fluid remains constant even though the volume of propelled fluids is varied provided the orifices through which the propelling fluid flows in the main tube and sidearm in the aspirating tube remain of constant cross-sectional area. Thus, if a unit volume of fluid, say for example one liter, is forced through the main tube of an injector and draws into the aspirating sidearm, say 1/10 of a liter of fluid, the ratio is 10:1. If the volume forced through the main tube is doubled (20 liters), then the aspirated
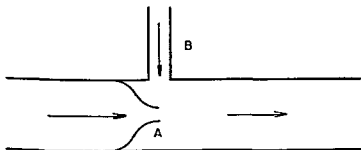

FIG. 24.1. A fluid driven through a constriction in a tube at a high flow rate (A) creates a sub-atmospheric pressure at this point. A sidearm (B) placed at this point allows another fluid to be drawn into the driving fluid and be mixed with it. The injector is constructed on this principle.
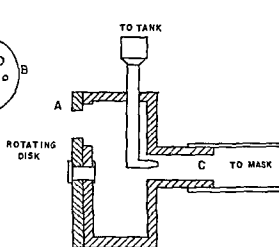
Fig. 25.1. Cross section of injector used for oxygen therapy. Oxygen is forced under pressure through the nozzle which creates a negative pressure and draws air through opening (A). Mixture of oxygen and air is delivered through outlet (C) to mask. Proportion of air is varied by adjusting size of openings rotating on disk. This is accomplished by constructing the face of the meter as a rotating disk with perforations of different sizes (inset B).

Fig. 26.1. The injector used for mixing air with oxygen for inhalation therapy.

volume is doubled (2/10 liters). If the flow is tripled the aspirated quantity is tripled also. The mixture issuing from the throat, then, maintains a constant percentage composition irrespective of the flow rate of the propelling fluid. The constancy persists regardless of the volume of the fluid passing through the main tube provided the aspirated fluid is supplied in unlimited quantities without impedance.

Viscosity of Fluids

If transparent tubes are placed vertically at the entrance and exit of a horizontal tube through which a non-compressible, frictionless, fluid is flowing the fluid rises in these tubes in proportion to the lateral pressure exerted on the wall of the horizontal tube. Theoretically the levels are identical in both tubes; actually, however, the level in the tube at the point of exit is less than in the one at the point of entrance (Fig. 27.1). A portion of the energy possessed by the molecules in the fluid is converted from kinetic to some other form, and is utilized for a purpose other than propelling the fluid. The fluid level in intervening additional tubes placed between these two declines progressively along the length of the tube. The energy lost by the moving fluid is used to overcome friction. This friction arises from two sources. One portion is caused by the contact of the molecules of the fluid with the surface of the tube; the other is due to internal friction, that is, friction of the molecules within the fluid. All fluids exhibit a certain degree of internal friction. The term *viscosity* is used to designate this internal friction of a fluid. When a fluid moves through a tube of uniform diameter the velocity of the molecules is not uniform throughout its mass. If the mol-

ecules could be visualized, those adjacent to and in immediate contact with the wall, a single layer, would appear to be at complete rest. The next layer moves, but sluggishly. The next moves more rapidly. As the center of the tube is approached, the molecules in each layer move with greater velocity, the molecules in the center moving the fastest. The forward advance of a row of molecules extending along the diameter of the tube would be represented by a parabolic curve (Fig. 28.1).

Poiseuille's Law

The volume of a fluid discharged through a tube varies with (1) the length of the tube, (2) the diameter of the tube, (3) the decline in pressure as the fluid is propelled along the tube, and (4) the viscosity of the fluid. A French physician, Poiseuille, studied the relationships of these factors to the volume of fluid discharge and summarized them in a mathematical expression known as *Poiseuille's Law*. The law states that the volume (q) of a fluid discharged through a tube of uniform diameter is equal to π r^4 divided by eight times the coefficient of viscosity (η) multiplied by the pressure difference (Δp) from one end of the tube to the other divided by the length of the tube (L). The equation would thus be written: $q = \dfrac{\pi \; r^4}{8 \; \eta} \cdot \dfrac{\Delta p}{L}$

The volume of discharge, as can be seen in the equation, is inversely proportional to the length of the tube and directly proportional to the fourth power of the radius of the tube. Thus, if the length of a tube is doubled, the volume of fluid discharged is halved if all other factors are constant. In order to maintain a constant volume of discharge the force

or pressure propelling a fluid through the tube must be, at least, doubled. When a tube has a radius of one centimeter, and this radius is reduced to one-half centimeter the volume discharged per unit time is $\frac{1}{16}$ of the original since it is a function of the fourth power of the radius—$(\frac{1}{2})^4 = (\frac{1}{16})$. A decrease of the radius to one-third of a centimeter reduces the flow to $(\frac{1}{3})^4$ or $\frac{1}{81}$ of the original discharge (Fig. 29.1). Thus, if a constant discharge is to be maintained, the propelling force must be increased 16 times in a tube having a $\frac{1}{2}$ centimeter radius
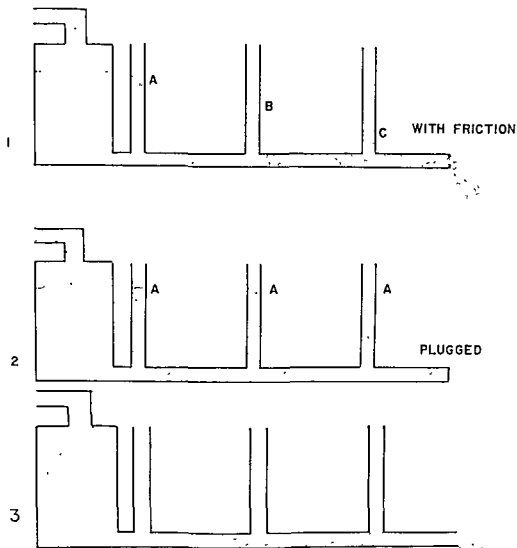
FIG. 27.1. Diagram illustrating friction head. A non-compressible frictionless fluid rises in proportion to the lateral pressure exerted on the wall of a horizontal tube. If the horizontal tube is sealed at one end the pressure will rise equally in all tubes (2). If friction is entirely eliminated there will be no lateral pressure and the fluid rises in none of the tubes (3) The fluid level in intervening tubes declines progressively along the length of the tube due to the loss of energy used to overcome friction (1).

Fig. 28.1. The forward advance of a row of molecules of fluids extending along the diameter of a tube is represented by a parabolic curve. The molecules move through the tube in layers. The molecules in each layer move with greater velocity as the center of the tube is approached. Those in the center move the fastest.
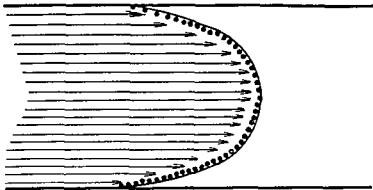
and 81 times in a tube having a ½ centimeter radius over that of one having a one centimeter radius. Obviously, decreasing the diameter of a tube, particularly one of fine bore, even slightly, causes a considerable reduction in flow rate. The importance of having apertures as wide as possible in canisters, masks and fittings of inhalers is obvious. A decrease in diameter of several millimeters in a cuffed endotracheal catheter introduces considerable resistance which necessitates an increase in respiratory effort if adequate ventilation is to be maintained.

Poiseuille's Law applies to laminar flows in tubes of large diameter only and does not explain volume discharges of fluids having turbulent flows. Poiseuille's Law applies to both gases and liquids. Fluidity is the reciprocal of viscosity.

Degree of Viscosity

Viscosity must be determined experimentally for a given fluid; it cannot be computed mathematically. A shearing *movement takes place as the various layers* of molecules pass one another in the direction of discharge. The internal friction of the fluid opposes the displacement of these layers. This friction is indicated in terms of the force required to move one plane surface past another when the space in between the two surfaces is occupied by the liquid being studied.

Viscosity may be absolute or relative. *Absolute viscosity* is expressed in terms of the actual force required to overcome internal friction. *Relative* (or specific) *viscosity*, on the other hand, is a comparison of the viscosity of one fluid with that of another under identical circumstances. The unit of absolute viscosity is called the *poise*, named after Poiseuille. The unit is the tangential stress required, per unit area, to produce a difference of velocity of flow between two parallel layers of a fluid a unit distance apart at a given temperature. The unit of viscosity (or poise) is equivalent to a force of one dyne per sec. per cm.[2] when the two layers are one cm. apart. The dyne is the quantity of force which accelerates a mass of one gram one centimeter per second per second. The *poise* expresses a quantity of force of far greater magnitude *than is ordinarily encountered in overcoming* internal friction of most fluids. Therefore, viscosity is expressed by *smaller units known as the centapoise* and the millipoise. The centapoise is 1/100 of a poise; the millipoise 1/1000 of a poise; and the micropoise 1/1,000,000 of a poise. Ordinarily viscosity is expressed in terms of relative viscosity, that is, the viscosity of the liquid is compared to that of water at 20°C. The viscosity of water at
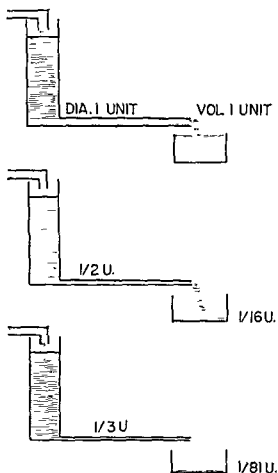
Fig. 29.1. The volume discharge of a fluid through a tube of varying diameter varies inversely as the fourth power of the radius, all other factors remaining constant.

An instrument known as a *viscosimeter*, devised by Ostwald, is used to determine viscosity. The viscosimeter consists of a capillary tube and a bulb attached to the capillary tube (Fig. 30.1). The fluid to be studied is drawn into the bulb and then allowed to pass down the capillary tube. The time required for a measured volume of the liquid to flow through the tube, at a given regulated temperature, is compared to the time required for the same volume of water to flow the same distance. Other types of viscosimeters are available, many of which are patterned after the one described by Ostwald.

The measurement of the viscosity of gases and vapors requires special apparatus. The viscosity of a gas or vapor may be determined by forcing a gas through a tube under constant pressure. In one type of apparatus a short column of mercury is allowed to fall through a

this temperature is designated as unity or 1.0.

In the assay of drugs, the mode of expressing viscosity differs somewhat from that used for precise scientific work. Instead of indicating viscosity in poises the kinematic scale is used. The *kinematic viscosity* is the absolute viscosity at a given temperature divided by the density of the fluid at that temperature. In other words, it is the ratio of viscosity to density. In the kinematic scale the units are called *stokes* or *centastokes*. The U.S.P. designates viscosity of drugs in terms of stokes.
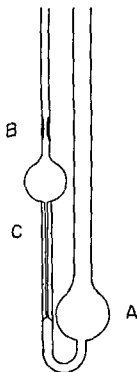

Fig. 30.1. The viscosimeter. The fluid to be tested is placed in bulb (A) and drawn as far as point (B). The time required for the fluid to pass from (B) to (C) is then determined and compared with that required for a reference fluid to pass the same distance.

glass tube between two points. The falling mercury drives the gas through the capillary tube under constant pressure. The time required for the mercury to fall the distance between the two points is used to compute the absolute viscosity. More frequently air is used as a reference gas and the relative viscosity is determined. Certain gases are more viscous than others, a fact of importance in determining the rate of effusion through a tube.

FACTORS INFLUENCING VISCOSITY

Temperature

Viscosity of a fluid varies with the temperataure. Liquids become less viscous as temperature increases. The viscosity of a liquid may be decreased as much as 2% for each degree Centigrade increase. The viscosity of a gas, on the other hand, increases with the temperature. The temperature at which the determination of viscosity is made must be indicated in expressing viscosity; otherwise the data is meaningless. Certain fluids flow through a tube more readily than others because they are less viscous.

Coefficient of Viscosity

The rate of discharge of a fluid is inversely proportional to its coefficient of viscosity. Thus, the volume of discharge of a fluid whose coefficient of viscosity is 4.0 is ¼ of one whose coefficient is 1.0 (Fig. 31.1).

Density

Viscosity is independent of the density of the fluid. Oxygen, which has a molecular weight of 32, has a coefficient of viscosity of 0.020 ($H_2O = 1$). Carbon dioxide, which has a molecular weight of
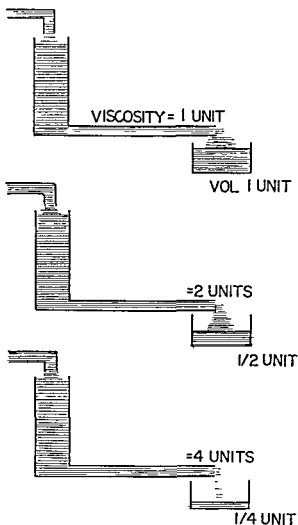

FIG. 31.1. The volume discharge of fluid moving through a tube varies inversely as its viscosity, all the factors remaining constant.

44, has a coefficient of viscosity of 0.015. The volume discharge of carbon dioxide through a capillary tube is greater than that of oxygen under ideal circumstances. Benzine and liquid petrolatum have nearly similar densities, but the petrolatum is more viscous and moves more slowly through a capillary tube. On the other hand methanol (S.G. .80) and chloroform (S.G. 1.5) differ widely in their densities but have nearly the same coefficients (.597 vs. .580) of viscosity. Their rates of flow through tubes of similar length and diameter are approximately the same at the same temperature.

Influence of Mixing Substances

The viscosity of a fluid is altered by combining foreign substances. Dissolving substances of high molecular weight increases viscosity as a rule. The viscosity of a solution of glucose or gelatine, for example, is greater than that of pure water. When ether is added to olive oil or water to molasses, the viscosity is decreased. The mixing of two gases of dissimilar viscosity likewise alters the viscosity.

EFFECT OF VISCOSITY ON DISCHARGE THROUGH ORIFICES

The influence viscosity has on the volume discharge of fluids through a tube is of importance in anesthesiology, particularly in regards to the measurement of gas volumes when using flow meters. The rate of efflux of a fluid through an *orifice* depends entirely upon density. The influence of viscosity upon the flow is negligible. On the other hand, the volume discharge of a fluid through a capillary tube is not appreciably influenced by density. Viscosity, however, becomes a dominating factor. The flow rate of cyclopropane can be measured accurately on a flow meter of the orifice type calibrated for carbon dioxide because their densities are nearly the same. However, the flow rates vary widely at the same calibrations in the tubular type (see Chap. 2).

QUANTITIES OF HEAT

UNITS OF HEAT CAPACITY

Heat transfer occurs in many of the physical and chemical processes involved in anesthesiology. A knowledge of some of the basic data concerning heat is necessary to clearly understand the physical phenomena which occur.

The amount of heat required to raise the temperature of one gram of water 1°C. is called a *calorie*. It is one-hundredth of the amount of heat required to raise the temperature of one gram of water from 0°C. to 100°C. It is designated by the symbol *cal.*$_m$. Often this quantity is referred to as a *gram calorie*, a mean calorie or a small calorie. One thousand small calories are often referred to as a *large calorie*. These large calories are used in physiologic and dietetic studies. The amount of heat required to raise the temperature of 1 pound of water at its maximum density 1°F. is called the British Thermal Unit or B.T.U. One B.T.U. is equal to 252 small calories. One calorie is usually standardized using water at 15°C.; the B.T.U is usually standardized at 60°F. The calorie is standardized at 15–16°C. because the heat capacity of a gram of water varies slightly at different temperatures. The 15° calorie is the amount of heat required to raise the temperature of one gram of water from 14.5 to 15 5°C. The symbol *cal.*$_{15}$° is often used to designate this unit of heat. The mechanical equivalent of heat or the amount of work necessary to produce a calorie of energy is known as the *joule*. The gram calorie 15° is equivalent to 4.185 joules. The mean calorie is equivalent to 4.186 joules. One joule equals 1.355 foot lbs. of work. The amount of heat required to raise the temperature of a unit mass of a substance at atmospheric pressure by one unit, that is, one degree, is called the *thermal heat capacity* of the substance. In most scientific studies, heat capacity is expressed in calories per gram per degree C. In engineering, on the other hand, the B.T.U. per pound per degree F. is used. Another term, often erroneously used interchangeably with thermal

capacity, is specific heat. The *specific heat* (designated by the letter C) of any substance *is the ratio of the quantity of heat required to raise the temperature of a unit mass of the substance 1°C. to the quantity required to raise the temperature of a unit mass of water 1°C.* The specific heat of water at 15–16°C. is expressed as unity (1), although at most other temperatures it is so nearly close to one that the differences are disregarded. The total *thermal capacity* of a body is determined by multiplying the mass of the body in grams by the specific heat of the substance. Gases differ from solids and liquids in regards to specific heat because consideration must be given to pressure or volume changes. Gases have two specific heats—a specific heat at a *constant volume* (C_v) and a specific heat at a *constant pressure* (C_p). When the *specific heat at a constant volume* is indicated, the quantity expressed is the heat required to raise the temperature of one gram of a gas 1°C. without changing its volume. The pressure, however, changes. *Specific heat at a constant pressure* on the other hand is the quantity of heat required to elevate the temperature of one gram of a gas 1°C. while it expands at constant pressure. The specific heat at constant pressure is the larger value of the two because an expanding gas does work at the expense of the heat contained by it. Gases have low specific heats and, therefore, absorb little heat, since the molecular concentration is rarefied. The significance of this is realized in considering the inhalation and insufflation of cold gases. The amount of heat abstracted is comparatively, speaking, little. Also, in bubble vaporizers, the amount of heat supplied by the ambient gases is, relatively speaking, insufficient to maintain adequate

vaporization. The specific heats of some gases and vapors expressed in calories per cc. are as follows:

Water	1.0
Liquid ether	0.36
Ether vapor	0.0016
Oxygen	0.0003
Air	0.0003

Liquids and solids possess higher heat capacities than gases. Water possesses one of the highest specific heats of common substances.

Some substances pass heat on from molecule to molecule more readily than others. This phenomenon, known as conduction, is of utmost importance, particularly in the design of vaporizers. The quantity of heat conducted in calories *per square centimeter for a thickness of one centimeter and a temperature difference of 1°C. per second is known as the thermal or heat conductivity.* This value is often expressed by the letter k. The conductivity of some common substances expressed in calories per centimeter at 0°C. per sec. are as follows:

Air	0.00057
Water (liquid)	0.0013
Copper	0.918
Silver	1.006
Aluminum	0.504

MOLAL HEAT CAPACITY OF GASES

Molecules of monatomic gases may move in three planes in space: (1) forwards and backwards, (2) sideways and (3) vertically. The combination of these three types of motion is referred to as *degree of freedom of motion* and represents all the energy of motion of a monatomic molecule. The molecules of a diatomic gas move in a more complicated manner. Each of the two atoms compos-

ing the molecule is able to move in the same three directions as does a monatomic molecule, but the movements in these directions are influenced by the restrictions of the interatomic attraction. If the atoms were free of this interatomic force, and the force did not interfere with movement, theoretically, the atom would be able to have six independent degrees of motion. However, in view of this force of intermolecular attraction, it has only five. A molecule composed of three atoms placed in a straight line will also have only five degrees of motion. If they are not in a straight line they may be capable of six degrees of motion. Molecules therefore may have diversified types of motion. The more types and direction of motion a molecule of a gas is capable of having, the greater will be the heat required to raise the temperature of the gas.

The quantity of heat required to raise the temperature of one mole of gas through 1°C. is known as the *molal heat capacity*. The molal heat capacity increases as the number and the weight of atoms in a molecule increases. The molal heat capacity of a gas is of interest because of the influence it may have in reducing the flammability of mixtures of anesthetic gases and vapors. Unless a spark is at the kindling temperature of an oxidizable substance it cannot initiate combustion. The addition of an inert gas which has a high heat molal capacity to a combustible mixture of gases or vapors may absorb such quantities of heat from a spark that it is cooled below the ignition temperature of the mixture. The mixture, thus, does not ignite. Gases with high thermal capacities, therefore, act as "quenching agents" by cooling sparks below the ignition temperature of a flammable substance.

VAPORS

DIFFERENCES BETWEEN GASES AND VAPORS

In most respects vapors behave like gases. They obey all the laws pertaining to gases such as Boyle's, Henry's, Graham's, Dalton's and so on. However, there are several points of difference in physical behavior which require mention. When the gaseous phase of a substance forms from the liquid phase at or below the boiling point of the liquid phase, the gaseous aggregate of the molecules is referred to as a vapor. If the temperature of a vapor is raised far above the boiling point or critical temperature of the liquid from which it is derived the molecular aggregate is referred to as a gas. A vapor exists close to the critical temperature of the substance from which it is derived. A *gas*, then, may be defined as a *vapor which exists far above the boiling point of its parent liquid*. Gases such as oxygen, nitrogen and helium are called permanent gases because at room temperature they are far above their respective boiling points and critical temperatures. A vapor may be liquefied by pressure without cooling; a gas cannot be. As a gas is compressed, and the critical temperature is approached, it becomes a vapor. The volume decreases as pressure increases. As the vapor nears its saturation point the pressure remains constant even though the compressing force is being sustained and energy is being added (Fig. 32.1). However, the volume rapidly decreases due to the condensation of the vapor and the transformation of the substance to its liquid phase. The changes in volume of a gas caused by pressure at a constant temperature, if plotted graphically, result in an equilat-

eral hyperbola. This type of curve has been referred to, previously, as an *isotherm*. As a gas approaches its vapor state, that is as it approaches the critical pressure, the curve shifts from a hyperbola to a straight line. This segment of the isotherm represented by a straight line represents a decrease in volume as the particles coalesce to form the liquid phase. The state of the vapor at this point is referred to as a *saturated vapor*. As soon as all the vapor has been converted to a liquid the pressure increases abruptly. The line on the graph rises steeply to indicate the increase in pressure. The volume at this point changes little or not at all since the substance is now a liquid and not compressible (Fig. 32.1).

VAPORIZATION

Liquids which boil below 60°C. and whose vapors possess anesthetic properties are considered sufficiently volatile for use as inhalation anesthetics. The principles of vaporization and a knowl-
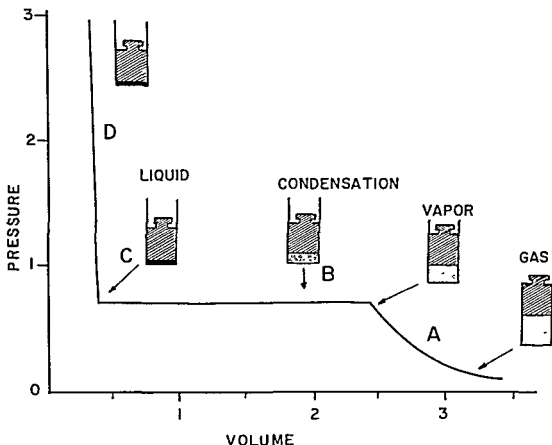
FIG. 32.1. Comparison of an isothermal of the gaseous and the vapor phase of a substance. At the constant state and temperature the volume decreases as the pressure increases, according to Boyle's Law, resulting in an equilateral hyperbola represented by the curve A. As the critical pressure is approached and the substance becomes a vapor the volume decreases as pressure is applied until the vapor condenses. The volume then decreases rapidly but the pressure remains constant until all the vapor condenses into a liquid. This is represented by the segment C-B. At C all the vapor has become liquefied. The segment C and D represents the shrinkage which is relatively small. Curve composed of A, B, C and D is known as an isothermal.
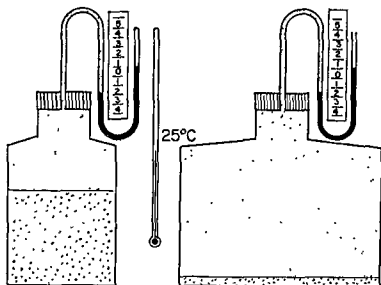
Fig. 33.1. A saturated vapor. The vapor pressure for a given liquid at a given temperature is always the same irrespective of the volume of fluid and the volume of overlying vapor.

edge of the methods of vaporizing volatile substances are important in anesthesiology. Molecules are constantly passing from the surface of liquids to the overlying atmosphere to form vapors by the process called *evaporation*. First, the fastest molecules at the surface escape. Eventually, there is a depletion of the supply of fast moving molecules. This depletion of fast moving molecules from the liquid lowers the average kinetic energy of the remaining molecules in the liquid. The temperature of the liquid remaining in the container falls since it is now composed of slower moving molecules. The speed of the escaping molecules of the vapor is reduced by the forces of mutual attraction exerted upon them by the molecules in the liquid as they move away from the surface. The vapor is thus cooled to the temperature of the liquid from which the molecules escaped.

Heat is absorbed during evaporation. The *heat of evaporation is the energy required to overcome the cohesive or attractive (van der Waals) forces of molecules* as they pass off as a vapor from the surface of a liquid. As the molecules of a vapor approach the surface of a liquid their speed increases because they are attracted towards the surface by the molecules of the liquid. Some pass into it. A gain in kinetic energy results as they approach and pass into the liquid. This is manifested by a rise in the temperature of the surrounding medium. The heat released to the surrounding medium is known as the *heat of condensation*. The heat of condensation of a given quantity of liquid at a given vapor pressure and temperature equals the heat of vaporization. The same amount of energy necessary to evaporate a given quantity of liquid is liberated when condensation of the resultant vapor occurs. The heat of vaporization of most liquids is less than that of water. When water condenses a considerable amount of heat is liberated. At 20°C., 585 calories are released; at 40°C., 574 calories.

VAPOR PRESSURE AND BOILING POINT

Molecules of a vapor exert a pressure in exactly the same manner as do molecules of a gas. Molecules of water in a

partially filled, corked bottle escape into the overlying air and exert a pressure in the same manner as does each of the molecules of the overlying air. The pressure of the water molecules is known as *vapor pressure*. When an equilibrium is established, that is, when as many molecules return into the liquid as escape from it, the atmosphere above the liquid is said to be saturated. The amount of a vapor, and, therefore, the vapor pressure, increases as the temperature of the water and overlying air rises. This is due to the fact that more molecules pass from the liquid as the velocity of the water molecules increases. A saturated vapor represents the maximum concentration of vapor which can exist for a given liquid at the temperature of the moment (Fig. 33.1). A saturation point, therefore, exists for a given liquid at each temperature. When the temperature of a liquid is raised to the point where the vapor pressure equals atmospheric pressure the liquid boils. The *boiling point* of a liquid is defined as the temperature at which the vapor pressure of the liquid equals atmospheric pressure. The boiling point of a liquid, therefore, depends upon the existing atmospheric pressure and varies with it. Boiling points are determined at normal atmospheric pressures. At the boiling point, the vapor escapes, not only from the surface, but, also from the interior of the liquid. Boiling differs from evaporation in this respect. Evaporation occurs at the surface of a liquid; boiling occurs from both the surface and interior. At less than normal atmospheric pressure all liquids boil at temperatures less than their normally assigned boiling points. At increased atmospheric pressures the boiling points are above their usual designated values.
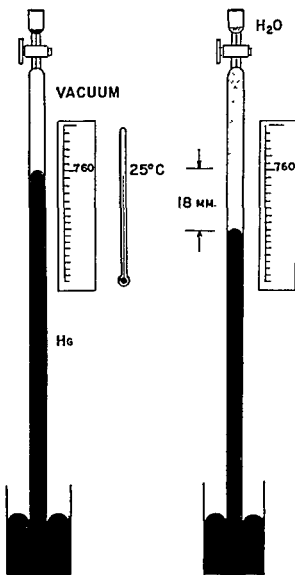
Fig. 34.1. Measurement of vapor pressures of liquids using a barometric tube. The liquid is introduced into the vacuum above the mercury and equilibrium is allowed to become established. The molecules of the vapor cause the column of mercury to fall in proportion to the pressure at that temperature.

THE HEAT OF VAPORIZATION

A liquid which is at its boiling point does not change its temperature until all the liquid has been vaporized, even though heat is being added. The heat necessary to vaporize the liquid is known as the *latent heat of vaporization*. The heat expressed in calories necessary

to vaporize one gram of water at normal atmospheric pressure at 100°C., its boiling point, is 537 calories. The heat of vaporization varies with the temperature at which vaporization occurs. The heat of vaporization increases for a given liquid as the temperature is reduced, and decreases as the temperature is raised. When the critical temperature of the liquid is reached the latent heat of vaporization is zero, since at that temperature the substance no longer exists as a liquid. The heat of vaporization of water, for example, at 0°C. is 595.4 calories per gram; at 200°C. it is 463.8 calories; at 365°C., the critical temperature, it is zero. More heat would be needed to vaporize a gram of water at 0°C. than would be needed at room temperature. The same principle applies to volatile liquid anesthetics. Water has a higher heat of vaporization than most liquids. The heat of vaporization of ether, for example, at its normal boiling point, is much less than that of water (83.9 calories per gram). Water differs from other liquids in having, not only a high thermal capacity, but also, a high heat of vaporization.

VAPOR PRESSURE OF LIQUID ANESTHETICS

A vapor, for example ether, overlying a liquid, for example water, dissolves in the liquid, if it does not combine with it, according to Henry's Law. The amount which dissolves is directly proportional to the partial pressure. Vapors dissolve in the water and obey the same laws as do the permanent gases. In order to be useful as an inhalation anesthetic, the vapor pressure of a volatile liquid at room temperature must be of a magnitude which results in the solution of a sufficient number of molecules in the plasma and cells to produce surgical an-

esthesia. Liquids which boil above 60°C., as a rule, are not suitable for inhalation anesthesia unless they are extremely potent because the vapor pressure is inadequate. Chloroform boils at 61°C. The drug would not be effective were it not for the fact that it is one of the most potent of the inhalation anesthetics. At an alveolar tension of 5 mm. Hg a sufficient number of molecules dissolve in plasma to produce surgical anesthesia. At 36°C. the vapor pressure of ether is 760 mm. Hg; at 25°C. when the vapor is at equilibrium with the liquid, it is 500 mm. Hg. A tension of approximately 30 mm. Hg is necessary to maintain anesthesia (Fig. 35.1). However, the 500 mm. Hg value represents the maximum tension possible at that temperature (25°C.) and not the actual one encountered clinically. In the open methods for vaporizing drugs, for example, tensions of 100–110 mm. Hg are rarely exceeded. Higher tensions are not attained clinically because the vapor is seldom at equilibrium with the liquid. Furthermore, in both the open and closed methods of administration the vapor becomes diluted with air and other gases used in conjunction with the drug. Besides, the vapor is being absorbed rapidly by the blood and tissues. During the induction of anesthesia an ether tension several times that necessary for maintenance must be used to saturate the tissues as quickly as possible to the point of anesthesia. This is described in more detail in Chapter 4.

DIFFUSION OF FLUIDS THROUGH MEMBRANES

PERMEABILITY OF MEMBRANES

The phenomenon of diffusion of fluids through permeable membranes was first observed by Jean Nollet in 1748. When

a membrane separates two solutions having a common solvent the molecules on one side intermingle with those on the other until equilibrium is established. Openings in membranes may vary in size. It is possible for the openings to be of a size which permits the passage of solvent molecules and not those of the solute. The solvent molecules pass inward and dilute the solution in an attempt to equalize the concentration. A force is generated by the migrating solvent molecules. Pfeffer in 1787 measured the force generated by molecular diffusion and called it *osmotic pressure.*

It is possible for the pores in a membrane to be large enough to permit small particles to pass, but not large ones. When a solution composed of large and small molecules is separated from their solvent by such a membrane, the large molecules do not pass through but the small ones do. Donnan, using a solution of the sodium salt of Congo Red and sodium chloride, noted the large Congo Red anion was unable to pass through a membrane with small pores but that the ions of sodium and chloride could pass easily. The solvent molecules (water) could pass in either direction. The total positive charges must equal the total negative charges on either side of the membrane, since there must be electrical neutrality. In such a system of ions, one of which is not diffusible which has reached equilibrium the concentration of sodium and chloride ions is asymmetric. The concentration of sodium ion is less on the side of the membrane not containing Congo Red while the concentration of the chloride ion is greater on this side. At equilibrium the product of the concentration of sodium ions and chloride ions on one side of the membrane equals the product of the concen-
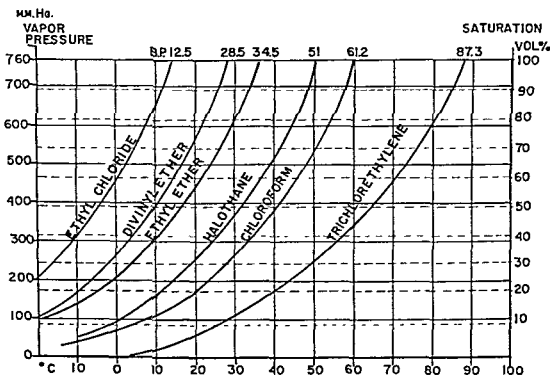
Fig. 35.1. The vapor pressures of currently used volatile anesthetics at different temperatures.

tration of the sodium, the chloride ion and the non-diffusible Congo Red anion on the other side. Since the concentrations of ions are different on either side of the membrane, an electrostatic difference develops between the interior and exterior of the membrane. The interior of the membrane is negatively charged while the exterior is positively charged. The magnitude of this difference in potential may be computed using the Nernst equation. This potential is proportional to the logarithm of the ratio of the concentrations of the sodium and chloride ions on each side of the membrane. At 19°C. when the ratio is 1:10 the potential is 58 millivolts. The state of ionic equilibrium may be represented as follows:

$$
\begin{array}{c|c}
\begin{array}{l} 4 \text{ Na}^+ \\ 3 \text{ C.R.}^- \\ 1 \text{ Cl}^- \end{array} &
\begin{array}{l} 2 \text{ Na}^+ \\ 2 \text{ Cl}^- \end{array}
\end{array}
$$
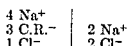
The potential difference which develops is the source of the membrane potential which is so important in biological systems and which will be referred to many times in succeeding chapters.

LIVING AND NON-LIVING MEMBRANES

Living membranes differ from non-living in one regard concerning this migration of ions. They can, by supplying energy derived from biological reactions occurring in the cell wall, move ions against a gradient. In other words, they can disrupt this equilibrium and transfer ions from an area of low concentration to a higher one and alter the potential difference. In fact, the potential may even be reversed. In non-living membranes the flow is from the higher gradient to the lower one. Once equilibrium is established it cannot be reversed unless concentrations are changed by re-

moving or adding ions from the entire system.

OSMOSIS AND OSMOTIC PRESSURE

DIFFUSION THROUGH MEMBRANES

The phenomenon referred to as osmosis is associated with the diffusion of substances through a semipermeable membrane. A cell is nothing more than a dilute aqueous solution of a variety of substances occupying a compartment surrounded by another aqueous solution of different composition. The cell is delineated from its environment by a semipermeable membrane through which some substances pass and others do not. The inward or outward diffusion of substances into the cell depends upon the differentials in concentration and the selective permeability of the membrane. A pressure develops within the cell as a result of such diffusion. This pressure is referred to as *osmotic pressure*.

APPLICATION OF GAS LAWS TO OSMOTIC BEHAVIOR

Substances in dilute solutions whether they are liquids, solids or gases behave almost precisely as if they were in a gaseous state. One gram molecular volume of a gas occupies a volume of 22.4 liters at 0°C. and exerts a pressure of one atmosphere. One gram molecular weight of any liquid or solid in its gaseous state would likewise occupy 22.4 liters and exert a pressure of one atmosphere if such a volume could be considered at 0°C. For example, the molecular weight of glucose is 180. The total molecules in 180 grams of glucose, if it were possible for them to be in a gaseous state, would occupy 22.4 liters at one atmosphere pressure and 0°C. The same number of molecules dissolved in 22.4

liters of water at 0°C. would, irrespective of the pressure of the water molecules, still exert a pressure of one atmosphere. The behavior of molecules of such solutions, therefore, would follow the gas laws. A gram molecular weight of glucose dissolved in 11.2 liters of water would, according to Boyle's law, exert a pressure of 2 atmospheres since the number of molecules remains the same but they now occupy half the volume. The same quantity dissolved in 44.8 liters of water would exert half an atmosphere pressure, since the number of molecules per unit volume would be halved. Gay Lussac's and Charles' Law would also apply to such situations. The pressure of the molecules in a dilute solution is proportional to the absolute temperature if the concentration remains constant. Dalton's Law, likewise, applies to these situations. Each substance in a mixture of several substances exerts, in a solution, a pressure independently of the other. The total pressure is the sum of the individual pressures. The forementioned statements are generally applicable to dilute unionized solutions. Deviations from this generalization occur as solutions become concentrated.

DETERMINATION OF OSMOTIC PRESSURE

If a closed bag composed of a membrane permeable to water molecules but not to glucose is filled with a dilute solution of glucose and surrounded by pure water, molecules of water pass inward and distend the sack. There are more molecules of water per unit volume outside the bag than there are inside. The gradient for water is from the outside inward. Work is done by the water passing inward and a pressure develops in the bag which can be measured with a manometer (Fig. 36.1). The diffusion
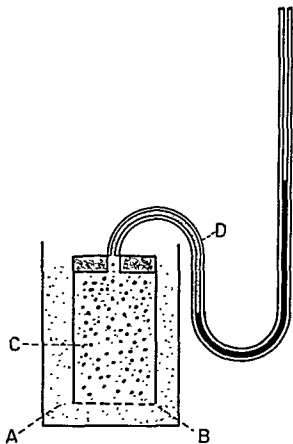
FIG. 36.1. Osmometer. The molecules of the solvent (A) pass through the semi-permeable membrane (B) and increase the pressure in chamber (C) containing impermeable solute molecules which causes mercury to rise into manometer (D). Rise in centimeters of mercury is equivalent to the osmotic pressure exerted.

pressure of the pure water molecules outside is greater than that of the water molecules of the glucose solution inside. This pressure is equal to that exerted by the molecules of glucose. The pressure which develops in the bag can be offset by connecting the bag with a cylinder and piston and applying pressure to the glucose solution. The inward diffusion of water molecules is thus stopped. The excess pressure which must be added to keep the water molecules out of the bag is called the osmotic pressure. The osmotic pressure, therefore, is this inward pressure which must be applied to pre-

vent this inward migration of solvent. A device for measuring such pressures is referred to as an *osmometer* (Fig. 36.1). This is a direct method of measuring osmotic pressure which is not easily done. Osmotic pressure, therefore, is determined by some indirect method, such as noting the depression of the freezing point of a solution or measuring the vapor pressure of the solvent.

Iso, Hypo and Hyper-tonicity

If, instead of water, the exterior of the bag is bathed by a glucose solution which is more concentrated than the one inside water molecules diffuse outward from the interior to the exterior. The pressure in the bag falls and the bag becomes partially collapsed. If the solution surrounding the bag is of identical concentration as that inside the bag, molecules of water diffuse in and out freely and no change in volume occurs. The concentration remains the same on either side of the membrane because the osmotic pressure is the same inside as it is outside the bag. Thus, it can be seen that molecules of a solvent separated by a permeable membrane pass from a less concentrated solution into a more concentrated one.

Basically, the living cell behaves in a manner similar to such a glucose filled bag. Surrounding a cell with dilute aqueous solutions of molecular concentrations less than those of the cell may cause distention or even rupture of the cell and subsequent necrosis. Solutions whose osmotic pressure is equivalent to that of the cells are called *isotonic*. Solutions surrounding a cell having molecular concentrations and osmotic pressures greater than that of the cell are called *hypertonic*. The cell loses water to its environment and slowly shrinks. This proc-

ess of shrinkage is called *crenation*.

The osmotic pressure developed by most biological fluids is due to a mixture of a variety of molecules dispersed in a solvent. Pressures of several atmospheres may be generated when cells are placed in environments which are not isotonic.

Effects of Ionization

The magnitude of the pressure developed depends upon the number of discrete particles in a solution. Size, weight or type of molecules have no influence. A lightweight molecule or an ion exerts equally as great a pressure as one exerted by a heavy, large, undissociated molecule. Therefore, a molecule of a substance like albumin exerts as much of a pressure as a molecule of glucose which has a molecular weight of 180 or an ion of sodium which has a weight of 35. A substance which ionizes actually exerts a higher osmotic pressure than would be expected if it did not ionize because of the presence of an increased number of particles per mole. A substance such as glucose which does not ionize has an osmotic pressure of a magnitude one would ordinarily expect or calculate from its concentration. The relationships between molar concentration and osmotic activity are expressed in terms of *osmols*. One gram molecular weight of glucose (6.02×10^{23}) molecules is termed one osmol. One osmol (180 grams) of glucose dissolved in 22.4 liters of water depresses the chemical potential so that a pressure of one atmosphere must be applied. Osmolarity equals molarity times the number of particles per mole resulting from ionization. The osmolar and molar concentrations of solutions of non-ionizable substances are equal. The laws pertaining to osmotic pressure were formulated by Van't Hoff.

EFFECTS OF NON-ISOTONIC
SOLUTIONS ON LIVING CELLS

The importance of injecting solutions whose tonicity is equal to those of the cells is obvious. Necrosis, hemolysis or edema may result from use of hypo or hypertonic solutions. The osmotic pressure of human cells at 37°C. is 0.3 of an osmol or 7.62 atmospheres. The same is also true of serum. As a rule, harmful effects are less frequent after the use of hypotonic than after hypertonic solutions, particularly if such solutions are administered intravenously. Presumably this is due to the fact that diffusion takes place quickly with hypotonic solutions and cellular rupture is not a serious problem. Intra and extracellular fluids seem well able to withstand low osmotic fluid pressure as long as the anatomical confines of the intracellular fluid are not restrictive. This applies particularly to the intravenous use of such solutions. Otherwise pressure necrosis results.

The injection of hypertonic solutions carries a greater possibility of disaster than the use of hypotonic, particularly when injection is made into the tissues. Such solutions cause migration of water when they come into contact with the cells. Dehydration and desiccation of the cell occurs. This results in death of the cell because the medium in which essential substances are stored, dissolved or utilized is withdrawn. The possibility of damage is lessened when such solutions are administered intravenously because dilution with plasma occurs quickly. Small amounts of hypertonic solutions therefore, may not be harmful. Osmosis and its relationship to injection of solutions into tissues is of particular interest in local anesthesia. This aspect of osmosis is discussed in Chapter 21.

Clinical Application of Physical Principles Concerning Gases and Vapors to Anesthesiology

MEASUREMENT OF PRESSURES

BASIC TYPES OF INSTRUMENTS

THE MEASUREMENT of fluid pressures can be a complex procedure which, in precise studies, requires elaborate devices. In clinical anesthesia, however, the problem is largely one of measuring gas pressures of reasonable magnitude with simple devices. Usually, this is accomplished by means of either *manometers or pressure gauges*. Two types of manometers may be employed, the *closed* (Fig. 2.2) and the *open* (Fig. 1.2). Both types consist of vertically arranged U-shaped tubes partially filled with a displacement fluid, usually water or mercury, in which the fluid rises or falls. Gauges are composed of diaphragms or membranes against which the force of pressure acts. They are distorted in proportion to the pressure and this distortion is translated into units of pressure.

UNITS OF PRESSURE

In the English system manometric pressures are expressed in inches of mercury or of water; in the metric system in centimeters of mercury or water (cm. Hg or H₂O). Gauge pressures and pressures of high magnitude are indicated in terms of force per unit area, such as pounds per square inch, grams per square centimeter or in terms of at-

mospheres. Pressures of small magnitude are expressed in millimeters of mercury or water. Water is used as the displacement medium in the measurement of small pressures. The distance to which is 1/13.6 that of water under comparable circumstances. One centimeter of water pressure equals 0.7 mm. of mercury. One centimeter of mercury pressure equals 13.6 cm. of water. Water manometers, therefore, are more "sensitive" than those using mercury as the displacement fluid. They are preferred when pressures of small magnitude are measured. Pressures ordinarily encountered in clinical anesthesia are small, particularly during intrapulmonic studies. Mercury manometers, even though calibrated in millimeters, are not sufficiently sensitive to detect significant changes in these studies.

Individual Types

OPEN MANOMETERS

The simplest form of manometer for clinical use is the modification of the open U tube. It consists of a calibrated slender glass tube, approximately 25 cm. in length, which is raised and lowered vertically in a transparent container in water. The manometer is connected to the anesthetic apparatus by a rubber

tube. The depth in centimeters or inches to which the mouth of the tube is submerged below the surface of the water indicates the pressure in the apparatus (Figs. 3.2, 4.2). The diameter of the tube is of no particular consequence if it is of sufficient bore to overcome the effects of surface tension on the base of the meniscus (0.25–0.5 cm.). This type of manometer may be used as an expiratory valve on certain types of apparatus in which positive pressure on the expiratory phase of respiration is desired (Fig. 5.2. It acts also, in addition to a manometer, as a safety valve in anesthesia and resuscitator appliances. The manometer is adjusted to the maximum desired pressure, and if this maximum is exceeded, the gas escapes from the mouth of the tube. The diameter of the container should be several inches wide so that the errors induced by changes in water level by the displaced water in the tube are minimal and of no clinical significance.

The U type of manometer is more satisfactory for studies requiring precision. This consists of a vertically placed U tube, one arm of which is connected to the apparatus, while the other is open to

FIG. 2.2. The closed type of manometer. The volume of air trapped in the sealed end expands or is compressed in proportion to the pressure exerted at the open end. The volume of the trapped gas varies inversely as the pressure, in accordance with Boyle's Law. The notations on the scale are spaced in inverse ratio to the changes in pressure.
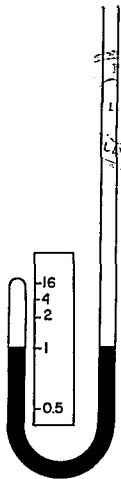
FIG. 3.2. A simplified water manometer for clinical anesthesia. The assembly consists of a T tube attached to the anesthetic apparatus. Adjustment is made by sliding the stem of the tube (A) through the top (B) of the container (C) along the calibrated scale (D) which is submerged in water. The pressure in the inhaler is equal to the number of centimeters the meniscus is depressed below the water surface. The gas escapes through (E) when the desired pressure is exceeded. The wide mouth container is used to minimize errors due to changes in water level.

FIG. 1.2. The open type manometer. Ordinarily mercury is used as the *displacement fluid.* Water is used as the displacing fluid instead of mercury when greater sensitivity is required.

FIG. 4.2. Manometer described in Fig. 3.2. The ratchet allows adjustment of the tube to the desired pressure. (Courtesy of Richard Foregger, Ph.D.)

other communicates with the apparatus (Fig. 2.2). The air trapped in the sealed end becomes compressed or expands in proportion to the pressure exerted on the surface of the liquid at the open end. The pressure and volume of the trapped gases vary according to Boyle's Law, if the temperature remains constant. Since the volume varies inversely as the pressure, the notations indicating units of pressure on the scale are spaced closer and closer together as the pressure increases. On the other hand, if the pressure in the apparatus is reduced below that of the gas in the sealed portion of the tube, the markings on the scale are spaced progressively farther apart as the pressure lessens. Small changes in pressure are reflected by increasingly greater spacings by the scale. The closed type of manometer is less sensitive for measuring increases in pressures than the open manometer. It is useful for moderately high pressures. It also may be used for measuring fine gradations of negative pressures. The absolute pressure may be measured by displacing the gas in the sealed limb of the U and permitting mercury to fill the seal. This type of manometer, known as the absolute manometer, is used when measuring subatmospheric pressures in laboratory studies. Commercially available absolute manometers measure pressures ranging from zero to —350 mm. Hg. However, by lengthening the limb to 80 cm., pressures ranging zero to —300 mm. Hg may be measured.

Barometers

The barometer is a closed type of manometer designed to measure changes in atmospheric pressure. Basically it consists of a tube 80 cm. long sealed at one end, filled and placed vertically with the open end submerged in a pool of mercury. The atmosphere, acting upon

the atmosphere Fig. 1.2). The pressure is indicated by the differences between the two levels of the contained fluid. Either mercury or water may be used, depending upon the magnitude of the pressures to be measured.

CLOSED TUBE MANOMETERS

The closed manometer consists of a U tube partially filled with mercury or other liquid possessing a low vapor pressure. The end of one limb is sealed; the

Fig. 5.2. Water manometer used for positive pressure oxygen therapy. Pressure is created during expiratory phase by exhaling against the resistance created by the column of water. The manometer also acts as an expiratory valve. (Courtesy Meyer Saklad.)

the surface of the mercury in the pool, normally elevates the column 76 centimeters into the evacuated tube. The space above the mercury is a vacuum save for the molecules of mercury vapor. If water were used as the medium, a tube 34–35 ft. long would be necessary because water is normally sustained to a height of 32 ft. in an evacuated tube by the atmosphere.

ANEROID MANOMETERS AND PRESSURE GAUGES

Manometers are not satisfactory for measuring high pressures; therefore, gauges are used instead. In a gauge, a metal diaphragm expands and contracts

as the pressure on its surface varies. The most common type used for anesthesia is the *Bourdon* (Fig. 6.2) type which consists of an oval shaped, hollow metal spiral tube sealed at one end. The other end is connected with the pressure source. The tube tends to become flat and elongated as the pressure of the gas admitted into it increases and resumes an oval shape and shortens as the pressure falls. A system of levers is activated by this change in length which in turn operates a clocklike indicator along a scale calibrated in units of pressure.

The Bourdon type of gauge has also been modified to measure pressures of small magnitude of the range ordinarily
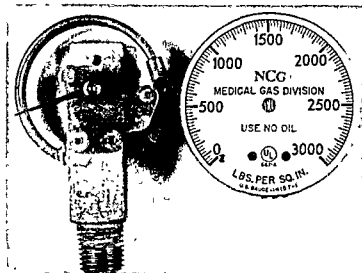
Fig. 6.2. The Bourdon gauge. The coiled tube becomes elongated and rounded when the pressure of the entrained gas increases, and shortened and flattened as it decreases. The changes in length operate a clock-like mechanism which translates them in units of pressure.

encountered in clinical work. These gauges are used in place of manometers. At times, such gauges are referred to as *aneroid* type gauges. The basic principles of construction are the same for these low pressure instruments as for the high pressure variety. The accuracy of these gauges at low pressures, however, is less than that of mercury or water manometers. Gauges which have been in service for long periods of time, particularly those which measure low pressures, become inaccurate, due to alterations in the metal from crystallization, changes in ductility and other physical factors. Such gauges should be calibrated periodically.

The *aneroid type of barometer* consists of a double pair of concave, thin metal diaphragms possessing a certain degree of elasticity which are sealed together trapping some atmospheric air between them. The pressure of the gases trapped by the diaphragms varies as the pressure of the atmosphere on the outer surface of the enclosure changes. The diaphragms bulge outward or are compressed inward. A system of levers is activated which records the pressure on

a recording kymograph in inches or centimeters of mercury.

Use of Tambours for Measuring Pressures

Tambours consist of diaphragms composed of rubber or other elastic substances stretched over a cup shaped structure which communicates with the pressure source (Fig. 7.2). In experimental studies tambours are used to measure pressures of small magnitude. They activate levers which write a record on a kymograph or move mirrors which cast a beam of light on a photographic plate. The accuracy and sensitivity of tambours vary widely and depend upon the elasticity of the diaphragms. There is a change in resilience with time and repeated use. Therefore, tambours must be recalibrated frequently.

COMPRESSED GASES

PACKAGING AND DISPENSING OF GASES

Gases, in order to be easily transported and available for immediate use, are compressed and stored in metal cylin-

ders. A compressed gas is defined as any substance which exerts a gauge pressure exceeding 25 lbs. per square inch at 70°F. Cylinders for anesthetic gases are constructed of steel with walls of a minimum thickness of ⅜″. In order to minimize weight, where this is a factor, some cylinders are made of alloys containing molybdenum or chromium. These weigh less and are stronger than steel. The Interstate Commerce Commission has formulated regulations concerning the construction, handling and filling of cylinders intended for interstate use. Cylinder sizes are designated by letters of the alphabet commencing from A. Size and capacity increase as the alphabet is ascended. Table I.2 summarizes the approximate content and the pressures of currently used gases according to cylinder size. Cylinders intended to be used at pressures exceeding 450 lbs. per square inch must withstand a pressure of 5/3 or 1.66 times the *service pressure*. The *service pressure* is the maximum pressure to which the cylinder may be subjected during ordinary usage. Thus a safety factor is established between the service pressure and the *absolute or maximum allowable pressure*. This is necessary in the event the gas expands should the cylinder be exposed to an excessively warm or hot environment. For example, an E cylinder designed to store oxygen, which, under ordinary circumstances, has a capacity of 400 liters of gas compressed to 2000 lbs. per square inch, must have sufficient tensile strength to withstand a pressure of 3400 pounds per square inch. In addition to tensile strength, cylinders must possess some elasticity. However, the expansion from this factor must not exceed 10% of a total possible expansion of the cylinder.
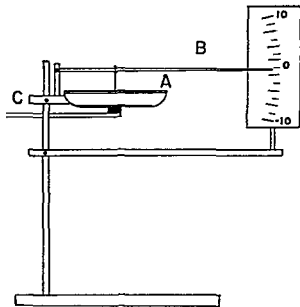
FIG. 7.2. A tambour used to measure pressures of small magnitude. Changes in pressure are transmitted to the diaphragm (A) which operates the lever (B). The apparatus is connected to the gas source at (C)

REGULATING AGENCIES

Gases used for medical purposes are prepared and packaged to meet the specifications of the Pharmacopeia of the United States. They are also subject to regulations of the Food and Drug Administration. Gases intended for interstate commerce must be packed in containers in accordance with regulations of the *Interstate Commerce Commission*. In Canada, cylinders used for medical gases must comply with the specifications of the *Board of Transport Commissioners*. Cylinders which have been in a fire must be removed from service until they have been properly reheated and retested. Records must be maintained summarizing data of tests on all cylinders.

CYLINDER VALVES

All cylinders are equipped with delicately constructed valves for filling and

TABLE 1.2

MEDICAL GASES—SPECIFICATIONS

Physical Properties	CO₂	CO₂O₂	CH₂CH₂CH₂	C₂H₄	He	HeO₂	N₂O	O₂
	Carbon Dioxide	Carbon Dioxide Oxygen Mix	Cyclo-propane	Ethylene	Helium	Helium-Oxygen Mixtures	Nitrous Oxide	Oxygen
Molecular Weight	44.01		42.08	28.05	4.00		44.02	32.00
Physical State in cylinder	Liquid	Gas	Liquid	Gas	Gas	Gas	Liquid	Gas
Spec Grav of Gas (Air =1)	1.529		1.481	0.974	0.138		1.531	1.105
Approx Press @70°F	800	1650–2050	75	1250	1650	1650	800	1650–2200
Critical temperature °C	31.34		124.65	9.51	−267.95		33.4	−118.84
Critical temperature °F	88.41		258.4	49.1	−450.3		95.7	−181.9
Critical Press. from gauge	1056.93		782.0	720.65	18.37		1087.5	715.84
Boiling Point °C	Sublimes		−32.9	−103.7	−268.9		−88.57	−182.97
	0–78.4							
Flammability Limits in Air			Low 2.40%	Low 3.05%				
			High 10.3%	High 28.6%				
Flammability Limits in O₂			Low 2.48%	Low 2.90%				
			High 60.0%	High 79.9%				
Oil/water Solubility @7°C			34.4	14.4	1.7		3.2	

Cylinder Fillings	Carbon Dioxide	Carbon Dioxide Oxygen Mix*	Cyclopropane	Ethylene	Helium	Helium-Oxygen Mixtures**	Nitrous Oxide	Oxygen
Cylinder Style A	12.5 oz 50 gals.	20 gals	AA** 9.25 oz 40 gals.	6.25 oz 40 gals	0.33 oz 15 gals.	15 gals	12.5 oz. 50 gals.	3.75 oz 20 gals.
Cylinder Style B	1 lb 9 oz 100 gals	40 gals.	BB* 1 lb. 7.25 oz. 100 gals.	15.75 oz 100 gals	0.63 oz 28 gals.	29 gals	1 lb. 9 oz. 100 gals.	7.25 oz 40 gals.
Cylinder Style D	3 lbs 14.5 oz 250 gals.	95 gals.	3 lbs. 5.25 oz 230 gals	1 lb. 15.5 oz. 270 gals	1.8 oz 80 gals.	82 gals	3 lb 14.5 oz 250 gals	1 lb. 1 oz 95 gals.
Cylinder Style E	6 lbs 9 oz 420 gals	165 gals		3 lbs 4 oz 330 gals	2.9 oz 131 gals.	134 gals	6 lb 9 oz. 420 gals.	1 lb 7.25 oz 165 gals
Cylinder Style F	20 lbs 1280 gals.	550 gals		10 lbs 12 oz. 1100 gals.	9.4 oz 425 gals.	435 gals.	20 lbs 1280 gals.	6 lbs 2 oz 550 gals
Cylinder Style M	31.25 lbs 2000 gals	800 gals.		15 lbs 14 oz. 1600 gals	13.7 oz. 605 gals	620 gals	31.25 lbs 2000 gals.	8 lbs 14 oz. 800 gals
Cylinder Style G	50 lbs 3200 gals.	1400 gals.		27 lbs 8 oz 2800 gals	1 lb. 8 oz 1100 gals.	1126 gals.	50 lbs. 3200 gals.	15 lbs 6.5 oz. 1400 gals
Cylinder Style H								20 lbs 4 oz 1825 gals.

* AA and BB are lightweight cylinders especially designed for use in cyclopropane service

** Weight depends on actual mixture.

sealing the contents. The valve must, of course, meet the same rigid standards required of the body of the cylinder. All cylinder valves are equipped with a safety device which permits the gas to escape if exposed to a hot environment. This guards against rupture of the cylinder which could follow from the increased pressure resulting in the event the cylinder is exposed to high temperatures. This device consists of a hollow bolt filled with an alloy which melts at a relatively low temperature. This bolt is usually placed in the valve stem (Fig. 8.2). The alloy is composed of Woods metal which consists of bismuth, lead, tin, and cadmium. It usually melts at 200°F. but the melting point may be al-tered by varying the proportions of the various metals.

TESTING OF CYLINDERS

A cylinder, at the time of manufacture, is subjected to the service pressure to which it will be exposed when in use. An automatic indicator records a graph of the testing pressure which must be sustained for a minimum of 30 seconds. A cylinder showing a drop in pressure during the test is rejected. Each cylinder is tested in this manner every five years or oftener. If found satisfactory it is continued in service; otherwise, it is rejected.

At each inspection cylinders are cleaned, the valve is removed and the

interior is washed with water. A spray of potassium hydroxide is next used which is in turn followed by a rinse of water, and then a spray of live steam. The interior is thoroughly dried. The valve, which has been tested, is reinserted. The cylinder is then ready for use once again.

MARKING OF CYLINDERS

The markings and labelings which are engraved in the metal at the shoulder of each cylinder are required by the Interstate Commerce Commission (Fig. 9.2). The following data are designated: the type of cylinder, the date the cylinder was commissioned, the service pressure, the dates of all tests, the insignia of the laboratory performing the tests, the identification number and the location of the manufacturer. Cylinders used for anesthesia are designated as type 3A. The usual service pressure is 2000 lbs. /sq. in. Cylinders which accommodate cyclopropane, for example, are rarely subjected to service pressures which exceed 75 or 80 pounds per square inch. Nonetheless, they are designed to accommodate pressures up to 2000 lbs./sq. in.

CARE OF CYLINDERS

Special care in handling cylinders is essential to assure safety. All cylinders must be stored in an upright position, in a cool place, and should be protected from heat, the sun's rays and chemical fumes. The room in which cylinders are stored must be adequately ventilated so that a complete change of air occurs once every 120 minutes.

The valve is the weakest and most delicate part of the cylinder. It is easily damaged by overturning or dropping a cylinder. Therefore, a rack, preferably one of metal or other non-combustible
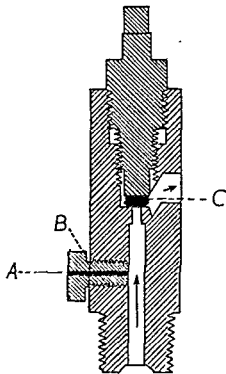
FIG. 8.2. Cross section through main cylinder valve showing arrangement to permit escape of gases from cylinders exposed to exceptionally high temperatures. The hollow bolt (B) is filled with an alloy (A) having a low melting point. The flow of gas is controlled by varying position of the valve seat (C).

material, should be provided for storing cylinders in an upright position. Metal racks of the "pigeon hole" type are available for storing cylinders in a horizontal position where conservation of space is a necessity. Large cylinders are provided with metal caps which are screwed over the valves to protect them in case they are accidentally upset.

Grease and oil should never be used on valves, gauges, threads for the cylinder cap or any piece of gas equipment used for anesthesiology. This is especially important when oxygen or nitrous oxide are being used. Both gases would support combustion of the grease. Special substances are available for lubricating purposes which have extremely high ignition temperatures and would,
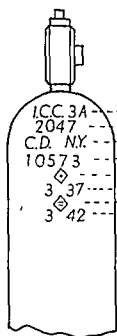
FIG. 9.2. The notations ordinarily found on cylinders used for anesthetic gases in clinical anesthesia. (A) Type of cylinder (according to classification of Interstate Commerce Commission). Cylinders used for anesthetic gases are designed as type 3A. (B) Service pressure. (C) Name and location of manufacturer. (D) Identification mark of manufacturer or proprietor of cylinder. (E) Identification mark of laboratory which tested the cylinder. (F) Date test was performed. (G) Identifying mark of laboratory performing periodic tests. (H) Retest date. Type of material and manner of construction of cylinder is sometimes indicated also.

therefore, be safe to use for clinical anesthesia.

TRANSFILLING OF CYLINDERS

Transfilling may be defined as the process of filling a cylinder of comparatively small capacity from a larger, reservoir cylinder. Cylinders should never be transfilled, particularly by individuals inexperienced in handling compressed gases. Certain anesthesiologists own small cylinders which they fill with gases purchased in bulk in large cylinders. Obviously, from a financial standpoint, this is advantageous, but, the hazard involved is great. Transfers of energy occur when a gas expands suddenly and is then recompressed, due, as has been mentioned previously, to adiabatic ex-

pansion and compression. A large quantity of heat may be evolved and a high temperature generated when a gas is recompressed in a brief period of time, particularly if recompressed in a small space (Fig. 10.2). The chance of overfilling with possible, subsequent rupture of a cylinder is another hazard of transfilling. Contamination or dangerous mixtures may also result if cylinders are not completely evacuated and cleaned prior to filling. Intermixing of flammable gases and vapors with oxidizing gases may also occur. The combustible substance may be ignited in the cylinder should heating occur during recompression. A cylinder designed to be used for one gas may inadvertently be filled with another—as, for example, oxygen with nitrous oxide. Cylinders owned privately by physicians are not under the supervisory control of the Interstate Commerce Commission, and, therefore, are not subject to the periodic inspection which all cylinders should undergo regardless of ownership. Defective valves and small cracks may be unnoticed in these privately owned cylinders. These may later lead to rupture of the cylinder with serious consequences.

Should one open the valve of a cylinder not attached to a yoke or reducing valve—a dangerous practice—he should do so with the outlet pointing away from the operator. Injury has resulted from failure to take this precaution. As the gas escapes from an open or damaged valve, there may be a backward thrust which may cause the cylinder to topple over and oscillate out of control over the floor until the contents are completely evacuated.

Even though a vacuum is applied to cylinders to completely exhaust them of all gases before refilling, it is good prac-
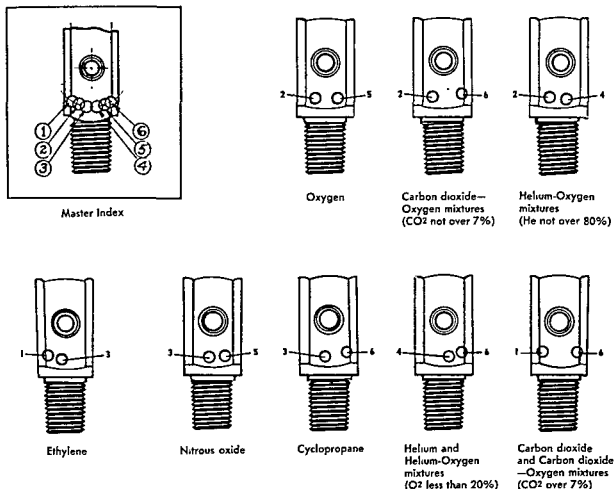
FIG. 10.2. The pin index system designed to prevent accidental interchanging of cylinders and the administration of the incorrect gases. The pins on the yoke match the holes on the valve of the cylinder. (Courtesy Ohio Chemical Company.)

tice to close all valves, whether empty or not, to prevent contamination with dirt and moisture.

COLOR MARKING AND LABELING OF CYLINDERS

At the suggestion of the U. S. Department of Commerce and the Bureau of Standards, color markings have been adopted for the identification of cylinders and their contents. The World Health Organization has recently adopted an international color scheme for identification. The colors listed in Table II.2 are now in use for identifying gases throughout the United States. It is cus-

tomary to paint the exterior of the entire cylinder with the designated color. If the cylinder contains a mixture of two or more gases, the colors of each gas are displayed along the body and shoulder of the cylinder. The same identifying colors are used for the labels. Chrome-plated cylinders which are not painted should bear labels which are of the color assigned to the gas.

The color scheme merely identifies the gases in the cylinders and not their concentration. For example, carbon dioxide and oxygen mixtures are available in the following concentrations in percent by volumes: 95–5, 90–10, 92½–7½, 70–30.

Chemistry and Physics of Anesthesia

TABLE II.2

The color marking of anesthetic gas cylinders recommended by the Bureau of Standards.

Oxygen.......	green (W.H.O., white)
Carbon dioxide ...	gray
Nitrous oxide .	light blue
Cyclopropane	orange
Helium .	brown
Ethylene ...	red (W.H.O., purp'e)
Carbon dioxide and oxygen..	gray and green
Helium and oxygen	brown and green

The color, irrespective of the concentrations of these combinations, is always the same—grey and green.

All cylinders should be labeled. The contents of an unlabeled cylinder should never be used. The label should bear the date of filling, the weight of the cylinder when full, the weight when empty, the contents in pounds and ounces as well as in liters or gallons. In addition the name and address of the manufacturer, the name of the gas, and qualifications regarding purity should also appear. Gases used for medicinal purposes are labeled U.S.P. if they meet the specifications of this body.

PIN INDEX SYSTEMS

The pin index system is a safeguard introduced to eliminate interchanging of cylinders and the possibility of accidentally placing the incorrect gas on a yoke designed to accommodate another gas. Two pins on the yoke are so arranged that they project into two matching holes on the face of the valve bearing the port (Fig. 10.2). The distances and positions of the two pins on the yoke and the holes on the valve are identical. Each gas or combination of gases has different distances and patterns of arrangement. Deliberate or unintentional attaching of a gas cylinder to a yoke intended for another is no longer possible with this system. For example, a cylinder intended for carbon dioxide has

holes bored on the valve to match the pins on the yoke designed to accommodate carbon dioxide. The pins and the holes match only carbon dioxide cylinders and carbon dioxide yokes. Should one attempt to place an oxygen cylinder on a carbon dioxide yoke, the oxygen cylinder will not fit the yoke because the pins do not match the holes. The pin index system is gradually being adopted throughout the United States. Manufacturers will no longer be able to interchange cylinders as they did in times of emergency or shortage and use one cylinder designed for a specific gas to package another gas. The pin index system is obviously designed to augment the practice of color identification, labeling and other safeguards and not to supplant it.

LIMITS FOR FILLING CYLINDERS

There is a limit to which distributors are allowed to fill cylinders with compressed gases. The limitations for filling cylinders with liquid agents differ from those for non-liquefiable gases. The allowable weight of liquid carbon dioxide is 68% of the weight of water necessary to fill the cylinder at 70°F. (21°C.). The limitation varies for each liquid agent. The limit for nitrous oxide is also 68%; that for cyclopropane is 55%. It is unsafe to exceed this limit because excessive pressures may develop if the cylinder is warmed. The vapor pressure of the liquid increases as the environmental

temperature increases. For instance, at 50°F. the pressure of a cylinder filled to the limit with pure liquid carbon dioxide is 638 lbs. per sq. in., at 70°F. it is 838 lbs., at 100°F. it is 1455 lbs. per sq. in. Should the cylinder be exposed to a still higher temperature, say for example, 130°F., the pressure will be 2365 lbs. per sq. in. Should more liquid be present than the allowable limit, the pressure could well exceed the maximum allowable for that cylinder, and rupture of the cylinder might occur if it is exposed to a high temperature. The maximum allowable quantity of drug in filling a cylinder is referred to as *filling density*. Filling density is defined as the percent ratio of the weight of the gas in a container to the weight of water the container holds at 70°F. Thus, a cylinder with an allowable filling density of 50% for a given gas could be filled with 10 lbs. of gas if its capacity were 20 lbs. of water at 70°F. The amount of a non-liquefiable gas which

may be placed in a cylinder may not exceed the service pressure of the cylinder at 70°F. In addition, the cylinder may not be filled with any gas whose pressure at 130°F. exceeds 1¼ times the service pressure.

Weight is the only exact index of the amount of a gas dispensed to a buyer. Pressure, however, is a reasonably accurate index of the quantity of a non-liquefiable *compressed gas* in a cylinder (Fig. 11.2). Gases which can be liquefied at room temperature and are dispensed as liquids, however, are purchased by weight. The pressure recorded on a gauge of a cylinder containing a liquefied gas is no index of the amount of agent present in the cylinder. The pressure of the vapor overlying the liquid remains nearly constant, at a constant temperature, until the last drop of liquid in the cylinder has evaporated. The vapor overlying the liquid in an E cylinder containing a quantity of nitrous oxide which is able to expand to 420 liters of
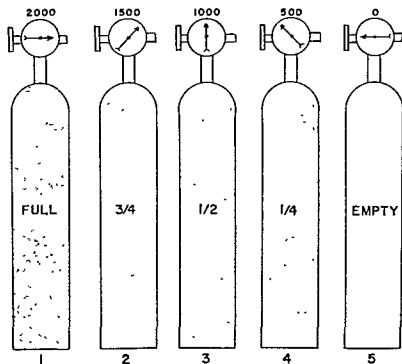
Fig. 11.2. The pressure of a compressed, non-liquefied gas decreases in proportion to the amount withdrawn from a cylinder.
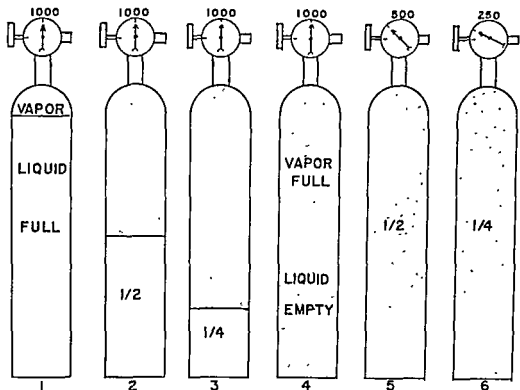
FIG. 12.2. The change in pressure in a cylinder containing a gas which has been lique-fied bears no relationship to the amount of vapor withdrawn. At a constant temperature the vapor pressure remains constant until the last molecule of liquid has been con-verted to the vapor state. The pressure then decreases in proportion to the amount of gas withdrawn. The vapor then behaves as a compressed gas. (See Fig. 11.2.)

gas at normal temperature and pressure exerts a pressure of 800 lbs. per sq. in. at 70°F. The gauge on a cylinder contain-ing the gas records 800 lbs. pressure when half the liquid has evaporated and passed from the cylinder. The gauge still records the 800 lbs. pressure when ¾ of the liquid remains. It continues to record this pres-sure until the liquid has evaporated com-pletely (Fig. 12.2). The pressure then falls in proportion to the amount of vapor withdrawn from the cylinder. The vapor remaining after evaporation of the liquid behaves like any other com-pressed gas and follows Boyle's Law. When half the volume has been with-drawn the pressure will be halved.

The situation is different when com-pressed oxygen is considered as the fol-lowing example illustrates: Assume that an E cylinder filled with sufficient oxy-gen to expand to 320 liters at standard conditions exerts a pressure of 2000 lbs. per sq. in. at 70°F. The oxygen exists as a compressed gas in the cylinder since its critical temperature is below 70°F. As the gas is evacuated from the cylinder there is a gradual reduction in pressure in proportion to the gas used. Thus, when 160 liters or half the contents are withdrawn, the pressure recorded by the gauge is one-half the original or 1000 lbs.; when 80 liters or ¼ of the original volume remains, the pressure recorded is 500 lbs. per sq. in. or ¼ the original (Fig. 11.2). Thus, the reduction in pressure is in direct proportion to the amount of gas withdrawn. The pressure of the nitrous

FIG. 13.2. The percentage of ether vapor delivered from a bubble type of vaporizer. The vapor pressure decreases as the temperature of the liquid falls. Curves were constructed from data obtained by using a ten liter flow rate of the propelling gas through the vaporizer.
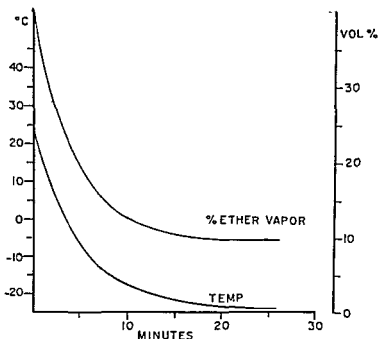
oxide vapor remaining in a cylinder after the liquid has completely evaporated behaves in exactly the same manner as oxygen does when it is withdrawn from the cylinder.

TEMPERATURE CHANGES IN CYLINDERS

When a gas under pressure is allowed to escape from a cylinder, through an orifice, cooling occurs. In the case of a compressed gas which is non-liquefiable at room temperature most of the cooling occurs at or beyond the valve. The cooling is due to the Joule-Thomson effect (Chap. 1). In the case of a gas which is liquefiable at room temperature which exists as a liquid in the cylinder, cooling occurs both at the valve and in the body of the cylinder. In this case, the cooling is due to two factors. The cooling at the valve is due to the Joule-Thomson effect as it is with the non-liquefiable gas. The vapor under pressure escapes through the orifice and behaves like a compressed gas. The cooling of the body of the cylinder, however, is caused by lowering of the temperature in the cylinder by the absorption of the heat of

vaporization necessary to convert the liquid into a vapor. Some of this heat is abstracted from the body of the cylinder. Cooling of the body is more obvious when the cylinder is in a cool environment than in a warm one. For example, when carbon dioxide is withdrawn from a cylinder in which the liquid carbon dioxide is at 30°C., the cooling of the cylinder is less pronounced than it is when the liquid is at 10°C. This is explained by the fact that the heat of vaporization of a liquid increases as the temperature of the liquid is decreased. At 30°C. the heat of vaporization of liquid carbon dioxide is almost zero because the temperature of the liquid at that point is near the critical temperature of carbon dioxide. At 10°C. the heat of vaporization of carbon dioxide is considerably greater and greater cooling occurs because more calories are required for vaporization.

STORAGE LOCATIONS FOR CYLINDERS

It is recommended that non-flammable oxidizing gases which support combustion, such as oxygen and nitrous

oxide, and inert non-flammable, non-oxidizing gases, such as carbon dioxide and helium, be stored separately from those which are flammable. The reason for this recommendation is that the oxidizing gases would accelerate the combustion of the flammable gases in the event of a fire because the cylinders would become evacuated when the Woods metal in the safety plug in the valve stem melts.

VAPORIZERS

UNDERLYING PHYSICAL PRINCIPLES CONCERNING VAPORIZERS

Vaporizers for liquid anesthetics are devices, the importance of which is frequently not appreciated. More often than not, their performance is variable and inefficient. The vapor tensions delivered to the patient are often erratic and subject to wide variations. In using gases the anesthetist has always known the quantity which was being delivered. Some metering device has always been used to acquaint the anesthetist with the concentration being delivered. This has not been the case with liquid anesthetics.

Two major difficulties are encountered with most vaporizers. (1) Unless a volatile liquid boils below room temperature and is potent, the vapor tensions delivered are less than those necessary to induce and maintain anesthesia. Difficulties are often experienced when using ether, chloroform or trichlorethylene because these liquids boil above average room temperatures (Fig. 35.1). (2) The concentration delivered is inconstant and varies from moment to moment in most vaporizers. If a vaporizer is to be efficient the heat of vaporization must be supplied steadily, as needed, otherwise the temperature of the liquid is decreased and the vapor pressure falls. Basically, there are two methods by which vaporization of liquid anesthetics is accomplished: (1) By warming the liquid above its boiling point and conducting the pure vapor directly into the apparatus. This is not necessarily the simplest and the most practical method but it is the one which approximates the ideal in providing a steady, unvarying concentration of vapor. (2) By simple evaporation. This is accomplished by exposing a small quantity of liquid over a large surface area and exposing this surface area to a moving gas stream. This permits more of the faster moving molecules in the liquid to escape as a vapor. The moving gas stream may be the patient's exhalation or a flow of gas from an external source.

EVAPORATION OF VOLATILE ANESTHETICS

Most vaporizers which employ the principle of evaporation, if used at temperatures below the boiling point of the liquid, deliver an initial maximal output when vaporization is first commenced. This is followed by a gradual decline towards a base level of vapor pressure. The temperature of the unvaporized liquid decreases and also tends to approach a base line. Vaporization is retarded because the necessary heat of vaporization is not supplied in adequate amounts from the environment. The latent heat of vaporization, that is, the number of calories necessary to vaporize one gram of a liquid, increases as the temperature falls. Thus, not only are more calories required for each gram of liquid vaporized at the lower temperatures, but the heat available in the unvaporized liquid is decreased as the temperature falls. Ultimately, if conditions remain unchanged, a point of equilibri-

um is reached. At this point both the concentration delivered and the temperature of the liquid reach constant values (Fig. 13.2). This point of equilibrium, however, is seldom attained under ordinary circumstances because as one environmental factor approaches equilibrium another which is at equilibrium becomes disrupted. There are two ways one can be assured of a constancy of vapor pressure in an inhaler. (1) The liquid is placed in a thermally isolated environment. If this is done the exact quantity of latent heat of vaporization necessary to deliver the desired concentration of vapor must be supplied (Fig. 14.2.) (2) The liquid is placed in an environment above the boiling point of the liquid and from which heat may be withdrawn as needed without limit. An excess of the pure vapor is thus provided at all times. However, this situation necessitates a device for measuring and controlling the flow rate of the vapor into the apparatus. The former conditions (absolute thermal isolation) are not easily attained. Vaporizers based upon the latter principle are available, however.

Type of Vaporizers

OPEN DROP TECHNIQUES

The technique of vaporizing liquid anesthetics ordinarily considered the simplest is actually the crudest and least efficient. This is the *open drop* technique. In this technique, the liquid is dropped, at as nearly a constant rate as possible, on a gauze supported by a metal screen or grid. The fibers in the gauze, due to capillary action, absorb the liquid in its meshes. Thus, a relatively large evaporating surface is created from a small amount of liquid. The inspired and expired gases are drawn over this surface. Vaporizers which utilize the movement of the patient's respired gases to evap-
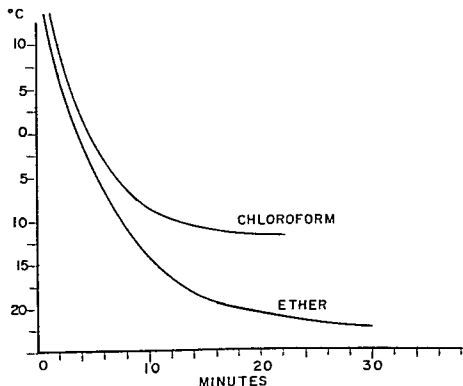
Fig. 14.2. The time required to attain the equilibrium temperature for 100 gm. ether and chloroform which are thermally isolated and through which 1000 ml. oxygen per minute at 23°C. are bubbled. (Courtesy of Albert Faulconer.)
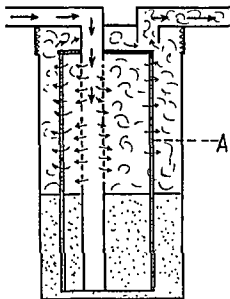
Fig. 15.2. Wick or draw-over type of vaporizer The vaporizer is introduced in a closed circle system either on the inspiratory or expiratory side The respired gases pass into the container over the wick saturated with the liquid Gases are warmed by the heat of the absorber. A manually operated bypass valve controls the amount of gas passing over the wick.

orate liquid anesthetics are often called the "draw-over type" of vaporizer. The open cone is the simplest of the *"draw over"* types. In the open cone, the necessary heat of vaporization comes from the respired gases, the supporting metal screen and the environmental air. The air, thus, serves both as a vehicle for carrying the gases and as the source of oxygen. During expiration, vaporization is accelerated because of the greater quantities of heat in the warm exhalations. Obviously, a sizeable portion of the vapor passes into the room atmosphere with the expired gases and is lost. On inspiration, the vapor beneath and over the mask becomes diluted with air. The inspired air is colder than the expired air. It is cooled further by passage over the cold gauze and screen. Vaporization on inspiration, therefore, is

slower than on expiration. Faulconer has measured the temperature which develops on the cone when ether is administered to an adult by the "open cone" technique and has found that it varies between —3° and —9°C. When ethyl chloride is vaporized, temperatures as low as —20°C. are often attained. It is obvious that the vapor tension in the "open cone" technique is inconstant and fluctuates with the expiratory exchange, the variations in temperature of the gauze, metal part of the mask, number of layers of gauze, the amount of liquid in the gauze at a given moment and the room temperature. Water vapor in the exhaled gases condenses on the mask, wets the gauze and retards vaporization, or it may even cause it to cease almost completely. Wet gauze on a mask, obviously, hampers any attempt to maintain a constant inhaled anesthetic vapor tension.

"Wick in Jar Type"

Closely allied to the open drop technique of vaporizing liquid anesthetics is the "wick in jar type" of vaporizer commonly found in the closed type of inhalers, particularly the circuit type (circle filter) (Fig. 15.2). This vaporizer consists of a wick supported by a wire frame, the lower portion of which is immersed in a transparent container partially filled with a liquid anesthetic. It could be considered an open cone enclosed in a jar. As in the open cone, the respired gases are drawn over the evaporating surface. It is, therefore, a draw over type of vaporizer. The liquid is drawn into and between the fibers of the wick by capillary action. The surface area and thickness of the wick are designed according to the volatility of the drug used. When vaporizing vinyl ether,

which is much more volatile than ethyl ether, a shallower container and shorter wick are used. The "wick in jar" vaporizer is placed on the exhalation limb of the circuit system in some "gas machines" and on the inhalation limb on others. When placed on the exhalation side the ambient gases pass through the container over the wick and back into the inhaler. A manually operated valve permits partial or complete by-passing of the exhalations to control the amount of anesthetic added to the inhaled mixture. When the vaporizer is placed on the inspiratory limb, the ambient gases are drawn from the breathing bag into the jar, over the wick and into the breathing tube. In this case, the gases may be warm, due to contact with the soda lime in which case the heat helps vaporize the drug. If the vaporizer is on the expiratory limb, the heat contained in the exhaled gases, if excessive cooling does not occur in passing through the

breathing tubes, may also accelerate vaporization of the liquid. The quantity of vapor delivered by this type of vaporizer is inconstant due to numerous variable factors. The variables which contribute to this inconstancy are (1) variations in the temperature of the exhaled or inhaled gases, (2) variations in the linear flow of the gases, (3) variations in the minute volume exchange of the patient, (4) variations in the surface area of the liquid presented to the exhaled gases, (5) variations in the temperature of the liquid, (6) variations in the length, size, and type of fibers in the wick, (7) the ease with which the heat of vaporization is transferred to the liquid from the external environment, (8) the depth of liquid in the jar, (9) the heat conductivity of the jar, (10) the temperature of the room and (11) the water content of the wick. In this case, as in the open cone technique, water condenses on the wick, and, in due time, vaporization ceases

Fig. 16.2. Temperature compensated vaporizer. Air is drawn into bypass (A) through opening (B) into vaporizing chamber (C) through outlet (D). Vaporization cools liquid (E) which causes element (F) to expand and contract proportionally. This in turn varies opening in outlet (B) increasing or decreasing amount of bypass. Permanent water jacket (G) assures adequate supply of caloric energy. Container (H) made of metal with high thermal conductivity is lined with wick (I) to enlarge evaporating surface. The Epstein, Macintosh, Oxford vaporizer is constructed in this manner.

EXHALE VALVE

←TO MASK

INHALE
-VALVE

BY PASS
INLET

AIR INLET

WICK

RESERVOIR

CAP
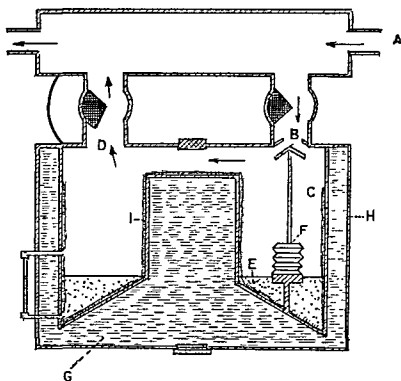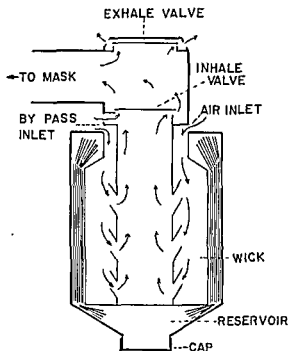
Fig. 17.2. Cross section of a semi-closed inhaler (Cyprane) used for administering mixtures of air and vapors of volatile liquids. During inspiration, air drawn through the ports over the surface of the wick lining the container vaporizes the liquid. The ports are adjustable and permit the bypassing of vapors so that the desired percentage of vapor and air may be adjusted. The liquid is stored in the bottom of the container. The Duke Inhaler is based upon the same principle.

unless wet wicks are replaced with dry ones.

In the last decade, the draw over type of vaporizers have been improved by adding automatic thermo compensators which cause the aperture in the by-pass valve to increase or decrease in size with changes in temperature (Fig. 16.2). The size of opening is increased when the temperature of the liquid in the reservoir drops and more of the gas is drawn over the evaporating surface. The aperture varies in size with the temperature of the liquid. A built-in water jacket and central compartment provides the necessary

heat since water has a high heat capacity. Wide fluctuations in temperature are averted. When ether is vaporized adequate compensation is obtained within the effective range of temperature for ether (16–33°C.).

Cyprane Inhalers

Certain vaporizers intended for the self administration of anesthetics (such as the Cyprane and Duke Inhalers used for trichlorethylene) are of the "wick in jar type" (Figs. 17.2, 18.2). Adjustable valves vary the amount of inhaled air which passes over a wick saturated with the liquid. The valve may be adjusted to a desired aperture size and locked. These vaporizers do not, as is believed, deliver a constant concentration of vapor. The concentration of vapor delivered, as in the other "wick in jar type," is higher, initially, than after use at a given setting. The concentration varies with the rate and depth of respiration, the amount of handling of the container (heat transfer from patient's hands), the environmental temperature, humidity and other variable factors. The concentration varies for a particular setting on a day to day basis. This is due to changes in environmental factors.

DROPPER TYPE

In using the dropper type of vaporizer the liquid is introduced directly into the inhaler, in the form of drops, from a cup-like reservoir. A manually operated adjustable needle valve regulates the number and size of drops delivered (Fig. 19.2). The liquid spreads into a thin film over a vaporizing surface. The vaporizing surface is usually a sheet of copper screen which has been rolled up concentrically. At times wicks are used but they are less satisfactory. The screen

Fig. 18.2. The Duke Inhaler for self-administration of vapors and volatile liquids.

is placed in the path of respired gases in the inhaler, usually close to the soda lime absorbers. As is the case of the "wick in jar" device, the concentration delivered is inconstant because vaporization is influenced by such variable factors as the linear flow of gases, the minute volume exchange of the patient and the environmental temperature. Much of the heat of vaporization is supplied by the reaction of absorption of carbon dioxide by soda lime. Vaporization is less apt to progressively decrease as the vaporizer is used as it does in the "wick in jar type" of vaporizer because of the greater availability of heat. One objection is the lag which occurs from the time of delivery of the droplets into the inhaler until they are all completely vaporized. If one could be assured that all the liquid being introduced into the inhaler is immediately vaporized, this device could be considered as being quantitative. However, some of the liquid is not vaporized immediately. It remains in the mesh of the screen, passes into the tubing and breathing bag and continues to vaporize after the flow from the reservoir has been stopped. The anesthetist would be aware of the exact volume of liquid delivered if this lag period were not a complicating factor.

BUBBLE TYPE

The bubble type vaporizer is the most widely used of all types. In this type, a
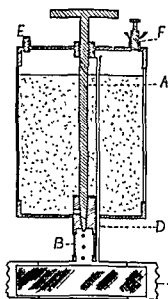
FIG. 19.2. Drip-per type vapori-zer. The liquid is divided into drops by the pin valve (A) which controls the vol-ume passing into the inhaler. The flow may be ob-served through the window (B). The drug is vaporized over a copper screen in tube (C) by the current of ambient gases in the inhaler. The tube (D) equal-izes the pressure over the surface of the liquid in the reservoir with that in the inhaler to per-mit a free flow. Vent (F) permits displacement of air by the liquid when filling container.

stream of a gaseous agent, usually air, oxygen or nitrous oxide, is broken into fine bubbles and passed through a col-umn of the liquid. The vapor passes off with the gas. The bubbles provide a large evaporating surface by creating a relatively enormous gas-liquid inter-phase (Fig. 20.2). The finer the bubbles the greater the evaporating surface pre-sented to the liquid. The bubble type vaporizer, as a rule, is the least efficient of the vaporizers. The quantity of vapor delivered fluctuates widely, due to such variable factors as (1) the changes in temperature of the liquid as evapora-tion proceeds, (2) the size and number of the bubbles, (3) the flow rate of the carrier gases, (4) the temperature of the carrier gases and (5) the depth of the column of the liquid through which the gas rises. This latter factor is a vital one since it determines to a large extent the duration of contact of the bubble with the liquid.

Bubble type vaporizers are often equipped with hot water jackets which are heated by electric hot plates to sup-ply the necessary heat of vaporization and to prevent the liquid in the reservoir from being cooled to the point of ineffec-tive vaporization. The bubble type of vaporizer is used extensively for insuf-flation and semi-closed techniques. As a rule, most bubble type vaporizers are not adequate for closed system anes-thesia because the volumes of gases nec-essary to vaporize the liquid are greater than can be accommodated by the in-haler.

The duration of contact of the bubbles of ambient gas with the liquid is rela-tively brief in the bubble types of va-porizer. Only a fraction of the theoretical capacity of the vapor passes into the bubble. Increasing the volume of am-bient gas through a vaporizer increases
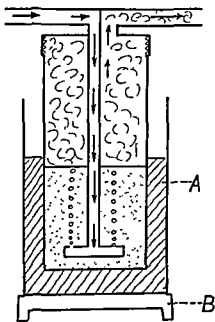
FIG. 20.2. Bubble type vaporizer. Gases di-vided into fine bubbles pass through the liquid. The vapor passes off with the gas. Jacket (A) contains warm water heated by hot plate (B) used to facilitate evaporation.

the amount of vapor delivered in the concentration in the mixture up to a point beyond which the percentage declines. At high flow rates the vapor concentration delivered may be less than at low, particularly after the vaporizer has been in use some time and the liquid in the reservoir has cooled. Even though the vaporization proceeds without change, as far as total quantity delivered is concerned, the concentration delivered at the higher flow rate may be less because, instead of becoming more concentrated, the mixture delivered may be diluted.

"Copper Kettle"

The heat necessary for vaporization of a liquid is supplied from the wall of the container which in turn is supplied from the external environment. Gases have low specific heats. The carrier gas supplies only a fraction of the necessary heat. Reservoirs in most vaporizers usually consist of glass jars. Glass has a low heat capacity and is a poor conductor of heat. Besides air has a low specific heat and, therefore, can transfer only a small fraction of the required calories to the glass. The process, therefore, quickly comes to a standstill. Thus, only a fraction of the calories necessary for satisfactory vaporization passes to the liquid. A container made of a substance which conducts heat rapidly and has a high heat capacity would obviate this objection. Metals would be more satisfactory. Morris has improved the bubble type of vaporizer so that it is quantitative in its delivery of vapor at low flow rates with little change in temperature of the liquid in the reservoir and the wall of the container. He employs copper for the container. The walls are massive. The interior, likewise, contains a solid, mas-

Fig. 21.2. New bubble type of vaporizer commonly referred to as the "copper kettle." The high thermal conductivity of copper permits transfer of heat from the environment to the liquid. The efficiency of this vaporizer is increased if it is mounted on a brass table top from which it readily absorbs the necessary heat.

sive core. The kettle rests upon the brass table top of the anesthetic apparatus. Copper has a relatively high rate of heat conductivity. The heat capacity (specific heat) is relatively speaking low 0.093 calories per gram. However, its density is 9.0. A cubic centimeter, therefore, weighs 9 grams and holds 0.81 calories which are readily transferable. This compares favorably with the heat capacity of one cubic centimeter of water which has a heat capacity of 1 calorie for the same volume. However, water is a notoriously poor conductor of heat. Therefore, the copper is able to rapidly absorb and transfer heat from its environment. The

flow rates heat utilization exceeds heat supplied. The temperature falls and the vapor pressure changes. Oxygen is used as the carrier gas. Oxygen for the metabolic needs of the patient is supplied by an additional flow meter provided for the purpose. Although designed primarily for the vaporization of ether for use in semi-closed inhalers the copper kettle may be used for other volatile liquids, such as halothane and in the closed system. Epstein and his associates have devised a vaporizer embodying the use of copper and water. A permanent water jacket composed of copper surrounds the ether reservoir Fig. 16.2). The copper draws upon the abundant stores of heat of the water to supply the necessary heat. A metal temperature compensator dips into the ether which contracts as it cools. This widens the port which admits more carrier gas into the vaporization chamber and compensates for the fall in tension of the vapor being supplied. Such temperature compensated vaporizers are being used more and more.

ATOMIZER TYPE

In some vaporizers, the gas is forced through a jet and the liquid is nebulized into a very fine mist which then evaporates to form the gaseous phase Fig. 22.2). The principles involved are the same as in the bubble type of vaporizer; namely, that a large evaporating surface is provided from which the molecules pass as a vapor. Instead of dividing the propelling gas into bubbles and passing them through the liquid, the reverse is done. The liquid is finely divided into small particles and presented to the gas. A gas-liquid interphase of a large surface area forms. The same quantities of energy are required for vaporization as

Fig. 22.2. E & J type of vaporizer. The ambient gas divides the liquid into fine droplets which evaporate and pass off with the gases.

heat transfer is largely from the metal table top and the frame of the anesthetic apparatus. Little is supplied from the air surrounding the kettle since air is a poor conductor of heat and possesses a low capacity. Morris has introduced one other modification of importance in the copper kettle. A sintered bronze disk known as porex is used to form the bubbles. These are extremely minute. Thus, a very small volume of gas may be converted to thousands of small bubbles and present an enormous surface to the evaporating liquid. The copper kettle is quantitative at flow rates not to exceed 250 cc. of gas per minute. At higher

if the gas were bubbled through the liquid. The same problems, namely, those of inadequate heat transfer and the use of high flow rate of ambient gas are present in this type as are found in the *bubble type vaporizer.*

Oxford Type Vaporizer

The Oxford type of vaporizer is designed so that a reservoir for the liquid is placed in an environment whose temperature exceeds the boiling point of the liquid (Fig. 23.2). The pure, undiluted vapor, *in measurable quantities, is thus delivered to the apparatus.* The situation is akin to that of using a liquefiable gas, such as nitrous oxide, in a container, in an environmental temperature above the boiling point of the liquid. Crystals of certain chemicals, for example hydrated calcium chloride or paradichlorbenzine, melt when placed in a container surrounded by a jacket filled with hot water. The container for the anesthetic is surrounded by the molten chemical. Thus, from within outward are the liquid to be vaporized, the chemical and the hot water. The chemical absorbs heat from the water and becomes molten. As the chemical solidifies, heat is liberated and imparted to the liquid anesthetic which is then heated above its boiling point. Solidification of the chemical occurs gradually so that all the heat is not released at one time. The chief advantage of such a vaporizer is that the volume of vapor delivered may be measured with a flow meter. The chief objections are that it is cumbersome and that vapor condenses in the flow meter and the mixing chamber unless they, too, are surrounded by the molten chemical and maintained above room temperature. After mixing the vapor with oxygen or other gases there is sufficient dilution
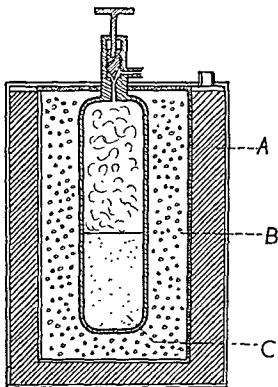
Fig. 23.2. Schematic representation of chemical heater used for volatilizing liquid anesthetics. The pure vapor is delivered because the temperature of the environment exceeds the boiling point of the liquid. The liquid is placed in the inner container (C). The outer container (A) is filled with hot water which melts a chemical, such as hydrated calcium or paradichlorbenzene in container (B). As the molten chemical cools it crystallizes and releases the heat of crystallization. This is imparted to the liquid to be vaporized. The flow of vapor is controlled by a valve. The quantity delivered may be measured by a flowmeter. The Oxford Vaporizer is based upon this principle.

to overcome condensation in the delivery tube, even though it is at a room temperature.

Deficiencies of Vaporizers for Liquid Anesthetics

The following are some of the difficulties and objections not previously mentioned which one encounters in using vaporizers and some of the precautions suggested when vaporizing liquid

anesthetics: (1) The use of heating devices for vaporizing liquid anesthetics may be hazardous, particularly in the "bubble" type of vaporizer. Undiluted vapors distill into the inhaler if the source of heat is not removed when the flow of propelling gas is discontinued. (2) The rate of oxidation of many liquid anesthetics is increased when the liquid is warmed, particularly when pure oxygen is used for insufflation. Peroxides and aldehydes may form from ethers and phosgene from halogenated hydrocarbons. These peroxides may ignite spontaneously or are toxic. (3) Gases forced through the liquid often contain water vapor which condenses in the reservoir and contaminates the liquid or wets the vaporizing surface. (4) Certain drugs, ethyl chloride for example, boil at unusually low temperatures. They cool the vaporizing surface below the freezing point of water. The exhaled water vapor then freezes on the mask. This may be avoided by reducing the volatility of the liquid or by lowering the freezing point of water. The addition of alcohol to the liquid prevents freezing of water on the mask.

HYGROMETRY

ABSOLUTE AND RELATIVE HUMIDITY

Hygrometry is that branch of physics concerned with the measurement of the quantities of water vapor in the atmosphere. The degree of saturation is called humidity. Humidity is absolute or relative. The mass of water vapor which is present, at a given temperature, at complete saturation in a unit volume air is known as the *absolute humidity*. Absolute humidity is expressed in terms of grams of water per liter of air (or other units of weight and volume) at a given temperature and pressure. As a rule, complete satuation of a mass of air with water vapor is not always attained. The ratio between the mass of vapor actually present in the atmosphere to that which the atmosphere is capable of holding, if saturated at a given temperature, is known as the *relative humidity*. Thus, if a unit volume of air at 20°C. and normal pressure is capable of holding four grams of water when saturated, but actually holds two, the ratio of theoretical capacity to actual capacity is 4:2 or 50% of complete saturation. Relative humidity is expressed in terms of percent saturation. Thus, a relative humidity of 50% at 20°C. indicates a given volume of air actually holds 50% of the vapor it could hold at that temperature.

Vapor Pressure of Water

The vapor pressure of water at its saturation point varies with temperature. The water content of the atmosphere increases as the temperature rises if sufficient water is available to saturate the air during the temperature rise. When the atmosphere is completely saturated with water vapor at a given temperature, the relative humidity is said to be 100%.

DETERMINATION OF HUMIDITY

Humidity may be measured with instruments known as *hygrometers*. Several types of hygrometers are available. These instruments operate upon *chemical* or *physical principles*. In the chemical methods of hygrometry, the quantity of water vapor is determined by passing a measured quantity of air through a series of previously weighed tubes containing a known weight of dehydrating agent such as calcium chloride or concentrated sulphuric acid. The chemical absorbs the water after which the tubes

are again weighed. This is a direct method which is highly accurate but too tedious and time consuming to execute for routine, clinical work. Freezing the water vapor with solid carbon dioxide and weighing the ice formed is an alternate method which may be used instead of chemical absorption. Less cumbersome, but admittedly less precise, methods have been devised for routine clinical application. The accuracy is sufficient for clinical and household purposes, however.

Dew Point

The relative humidity of a given mass of air decreases as the temperature rises and increases as the temperature is lowered if the vapor content of a unit mass of air remains nearly constant. If the temperature is lowered sufficiently, a point is reached at which the relative humidity becomes 100%, at which point condensation occurs. The water molecules become too numerous to remain in a vapor state at that temperature. They lose speed, come closer together and coalesce. The temperature at which condensation begins is called the *dew point*. Tables and graphs have been prepared

FIG. 24.2. Apparatus for determining dew point. *Air is bubbled through an easily volatilized liquid, such as ether, in a thin walled vessel. The temperature of the liquid falls and cools the wall of the container. The moisture in the atmosphere condenses on the exterior when the temperature of the glass wall reaches the dew point.*

from data obtained by direct chemical methods. From these the relative humidity of atmospheric air may be interpolated if one knows the temperature of both the atmosphere and the condensing surface. Humidity may be determined by the method of dew point. Dew point may be determined as follows: A current of air is blown through ether or some other highly volatile liquid contained in a thin walled receptacle (Fig. 24.2). The evaporation cools the liquid which in turn cools the surface of the container. When the temperature of the wall of the container is reduced to the dew point, the water vapor condenses on the outer surface. Thus, after determining the temperature to which the atmospheric air must be cooled to cause condensation of the contained water vapor, the relative humidity may be determined by referring to the prepared tables. This type of hygrometer was devised by Regnault.

Wet-Dry Bulb

The most common and practical method of determining relative humidity for clinical purposes is by the use of a hygrometer composed of a *wet and a dry bulb thermometer* (Fig. 25.2). *Two* thermometers of identical construction are mounted side by side. One is exposed to the atmospheric air; the other has wrapped about its bulb a wick which is moistened and extends into a vessel *containing water. The bulb of the "wet"* thermometer is constantly moist due to the capillarity of the wick. This type hygrometer is also called a *psychrometer*. In an atmosphere of low relative humidity, the water evaporates rapidly and causes a marked fall in temperature on the "wet" thermometer. A difference thus exists between the readings of the

Chemistry and Physics of Anesthesia
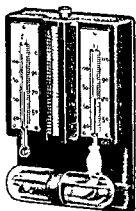
FIG. 25.2. Wet-dry thermometer used for determining humidity. (Courtesy of Richard Foregger.)

"wet" and dry bulb. In an atmosphere which is saturated with water vapor, evaporation proceeds slowly or not at all. The difference in temperatures registered by the two thermometers, then, varies only slightly or not at all. Here again, one refers to tables prepared by using a chemical hygrometer. The temperature differences and the temperature of the dry bulb may be interpolated in terms of percent saturation. The drier the air, the more rapid the evaporation and the greater the differential between the two thermometers. The air must be passed over the wet bulb at a substantial velocity in order to obtain valid measurements—a minimum of 900 ft. per minute.

Miscellaneous Methods

Other devices for determining the moisture content of atmospheric air utilize fibers of human hair which change length as they gain or lose moisture. This change in length operates a system of levers which is translated in terms of relative humidity on a clock-like scale. The continuous recording hygrometers operate on this principle. An inkwriting lever makes a record on a clock-like scale. The fine, well constructed of these may be extremely precise. The common ordinary varieties for household use are

grossly inaccurate, as a rule, and not satisfactory for clinical use.

Other methods of hygrometry employ certain types of crystals which dissolve in moist air and precipitate in dry air Others use chemicals which have one color in moist and another in dry air. Cobalt compounds, impregnated on paper for example, are pink in moist air and blue in dry air. None of these is sufficiently sensitive or accurate for clinical purposes. Measuring the thermal conductivity using a Wheatstone Bridge, or measuring the electrical resistance of salt films may also be used to determine humidity. Variations are proportional to moisture content. These methods are not practical for clinical use.

HUMIDIFICATION

Humidification is the addition of water vapor to anhydrous gases. It is an essential and an indispensable part of anesthesiology and inhalation therapy. Most compressed gases are anhydrous, and, unless humidified cause desiccation of the mucous membranes.

VAPOR PRESSURE OF WATER IN AIR AND TISSUES

It has been mentioned previously that water molecules pass from the surface of water exposed in a vessel to the overlying air. The partial pressure exerted by the molecules of water vapor depends upon their number, which in turn, depends upon the environmental temperature. In a closed system an equilibrium is established so that, at a given temperature, as many water molecules return to the liquid as escape into the overlying air. The air, then, is saturated. The weight of water vapor per liter of saturated air varies with the temperature. A liter of anhydrous air is heavier

than a liter of moist air. A gram molecular volume of water vapor weighs 18 grams; one of air 28.83 grams. Each water molecule displaces a heavier oxygen or nitrogen molecule in a given volume of air in the process of humidification. This accounts for the decrease in weight, since water is lighter than either nitrogen or oxygen. This also explains the reason for the decrease in barometric pressure noted when the air becomes moist prior to a change in weather.

The tension of water vapor in the pulmonary alveoli at 37.5°C. is 47 mm. Hg. The tension of water vapor in inhaled air and other gases is always less than 47 mm. Hg because these gases are at room temperature and do not, even if saturated, contain as much water vapor as air at body temperature. At 21°C., for example, the vapor tension of water is 18.6 mm. Hg. Consequently, even if inhaled air is 100% saturated it contains less water than the lung air. As it becomes warmed it can take up more water. Some water vapor would be lost from the tissues if it remained in contact long enough. However, it would not be as much as if the air were dry. In closed systems designed for total rebreathing in which alkali is used to absorb carbon dioxide the relative humidity is close to 100%. This is due primarily to the liberation of water by the neutralization of carbonic acid by the hydroxides during absorption. Some of the water vapor also comes from the exhaled air. However, the temperature is still less than 37°C. and the pressure gradient for water vapor is still from the lungs to air. Humidification is not necessary in units designed for total rebreathing because the water loss is of small magnitude and is tolerable. Techniques of inhalation therapy, particularly those utilizing insufflation and the semi-closed inhalers, in which anhydrous gases are used at high flow rates, require humidification if used for protracted periods of time.

METHODS OF HUMIDIFICATION

Humidification of inhaled gases may be accomplished in one of three ways: (1) The gas may be divided into fine bubbles and passed through a column of water. The principle involved is identical to that underlying vaporizers for liquid anesthetics. This is the most common method and will be discussed in more detail later. (2) The water may be divided into fine particles by a fast flowing stream of gas by using a nebulizer. Water and other liquids divided into fine particles in such a manner are referred to as *mists*. (3) Steam may be allowed to come into contact with cold air so that it condenses into fine particles of moisture. Such a condensation of moisture particles from a vapor is called a *fog*. Tovell and his associates have produced fog for therapeutic purposes by causing live steam to intermingle with air drawn over a refrigerating unit.

Size of Moisture Particles

Moisture in the air is invisible unless it is present in the form of a fog or mist. Visible fog contains particles from a fraction of a micron up to 40 microns in size. Mists may contain particles up to 100 microns in diameter. The particles of moisture in fogs and mists tend to settle out or coalesce into larger drops which fall out of the gaseous phase. If mists and fogs are inhaled, particles of 30 microns diameter or larger are baffled out in the nasopharynx and the trachea, those between 10 and 30 microns pass into the terminal bronchioles, those between 3 and 10 microns pass into the

alveolar ducts and those between 0.5 and 3 microns pass into air sacs. Those smaller than 0.5 pass in and out of the air sacs because they are light. Solutions of detergents and various drugs may be nebulized and inhaled. Fogs are used for moistening the mucous membranes and fluidifying secretions.

Bubble Humidifiers

Humidification of gases by bubbling them through water is rarely complete because vaporization proceeds slowly. The heat of vaporization of water is higher than it is for most liquids so that heat exchange, particularly if glass jars are used, proceeds slowly. The vapor pressure of water at room temperature is low compared to other liquids, such as ether, because the boiling point is considerably higher. The size and number of the bubbles, the depth of the column of water through which they pass, the duration of contact with the water and the temperature of both the gas and water are important factors. Evaporation of the water occurs at the surface of the bubble. The more bubbles which form from a unit volume, the greater the surface from which evaporation occurs. A disk with multiple perforations is ordinarily used for most humidifiers. Some have a porous metal or stone disk. This causes the formation of a multitude of extremely fine bubbles. The greater the number of bubbles, the greater the evaporating surface. One may understand how enormous a surface is obtained by subdivision of a particular volume of gas from the following example: One cc. of a substance contained in a 1 cm. cube would have a surface of 6 square centimeters. If this is divided into one millimeter cubes, one thousand cubes would result. Each of the thousand resulting cubes has an area of 6 square milli-

meters. A total surface of six thousand square millimeters would, therefore, result. Even though gas bubbles are spherical, and the surface per unit mass is less than that of a cube of equal volume, the same principle of such a subdivision would nevertheless apply. The efficiency of humidifiers, therefore, can be increased by dividing the gas into extremely fine bubbles and passing them into the humidifying jar. An index of the efficiency of humidifiers can be judged by the amount of water they vaporize in relation to gas flow. Obviously, a humidifier is inefficient if the water slowly disappears or does not disappear at all.

The following is an example of the amount of water used in a humidifier. The vapor pressure of water at 21°C. is 18.65 mm. Hg. If the relative humidity were 50% the vapor tension would be 9.32 mm. Hg. At 760 mm. Hg atmospheric pressure this is approximately 1.2% of the total or .0087 grams of water per liter of air at this temperature and relative humidity. A flow of 5 liters of oxygen per minute should evaporate 2.4 grams of water per hour to maintain a relative humidity of 30% at 21°C.

Some anesthetists have the misconception that hydraulic ("wet" or aqua) flowmeters humidify gases as well as meter them. This is true to a limited extent in the "sight feed" flowmeter because the gases bubble through water. The water depression type of meter exposes little or none of the ambient gas to the water. Therefore, no appreciable humidification occurs in this type. In such a flowmeter the water level changes slightly, if at all, even through prolonged, intense use.

MEASUREMENT OF GAS VOLUMES

The accurate metering of gases is necessary to insure mixtures of proper

proportions. The importance of this in anesthesiology and inhalation therapy is obvious. There are a variety of methods and instruments available for measuring gas volumes. In anesthesiology and in inhalation therapy gas volumes must be measured as gases are being withdrawn from a reservoir. The rate of flow is determined by devices called *flowmeters*. These will be described further on.

Gases Which Are Static

Gases which are static are usually measured by a variety of methods. One of the commonest is to use the *displacement* technique. A buret is filled with a displacement medium, such as water or mercury. The gas passes into the buret and displaces the water or mercury. In physiological studies, respired gases are measured by means of *spirometers, calibrated bags* or *bellows*. These techniques are described in text books on methods of clinical research and will, therefore, be omitted from this discussion.

Ambient Gases

Flowmeters used for industrial and engineering purposes differ from those used in anesthesiology. The so-called *test meters* are composed of bellows of equal volume contained in a metal receptacle. The gas passes into one bellows and forces the other to contract. When the first bellows fills it trips a lever and the stream of gas is then diverted to the second bellows. The movement of the bellows operates a mechanism which records the volume which passes through on a dial. The *thermoanemometer* is also used in industry. It utilizes the principle that the electrical resistance of a metal is a function of the temperature. A wire heated by supplying it with an electrical current at a constant rate and voltage is inserted into a flowing gas stream. The wire is cooled below its normal temperature by the ambient gas. The degree of cooling depends upon the temperature, specific heat and velocity of the flowing gas. This temperature change can be translated into terms of gas flow. Flowmeters based on the Venturi principle are used to measure bulk flow. Magnetic flowmeters are also available. However, none of these devices is applicable clinically.

Flowmeters Used in Anesthesiology

In the flowmeters used for anesthesiology a gas is allowed to pass through an orifice. A pressure difference results which is translated in terms of flow rate. A knowledge of the physical principle concerning gases, discussed in the previous chapter, is necessary to understand the manner in which flowmeters operate. In medical practice and in anesthesiology, in particular, gas flow rates are expressed in liters or cubic centimeters of flow per minute. The practice of expressing flow rates in gallons per hour, common heretofore, has fallen into disuse in the United States in anesthesia practice.

TYPES OF FLOWMETERS

Flowmeters used in clinical anesthesia are of two basic types. The first type is referred to as the *fixed orifice type*. It is also known as the variable pressure difference type and the fixed area type. This type consists of a tube with a constriction which is a true orifice interposed between the source of the gas and the point of delivery. A difference in pressure develops between the two sides of the orifice as the gas flows through it. This pressure difference is measured by some device, usually a manometer or a pressure gauge placed at the upstream part of the tube proximal to the orifice.

The pressure difference increases with the flow rate. The units of pressure difference are translated into terms of flow rate. The markings on the pressure measuring device are in terms of flow rate and not of pressure.

The second type is referred to as the *variable orifice type*. It is also called the fixed pressure difference type, the variable area type or the inconstant orifice type. This type consists of a tube with an orifice whose cross-sectional area varies. The pressure difference on either side of the orifice remains constant. The variations in orificial diameter are determined and translated in terms of flow rate. The manner in which this is accomplished is discussed later. Most flowmeters used for clinical anesthesia and inhalation therapy embody one or other of these two basic principles.

EFFECTS OF DENSITY AND VISCOSITY ON FLOW RATES

Many factors influence the accuracy and precision of flowmeters. In the fixed orifice type the nature of the constriction is important. If the thickness of the orifice (length) is negligible compared to the diameter, the obstruction may rightfully be classed as an orifice. The flow rate, then, is influenced by the density of the gas; viscosity plays a minor role. Should the constriction be elongated, and, instead of being an orifice, be a narrow tube, the flow rate would be influenced to a large extent by viscosity and, to a lesser extent, if at all, by density. In either case, the passage of the molecules is impeded and the pressure proximal to the constriction increases and continues to increase as additional gas is admitted from the source of supply. Carbon dioxide (M.W. 44) and cyclopropane (M.W. 42) are nearly alike in regards to

density. Their (relative) viscosities compared to water, however, differ considerably, being 0.015 and 0.0057 respectively. Nonetheless, their flow rates through orifices of the same diameter, under comparable conditions, are nearly alike. On the other hand, a mixture of 80% helium and 20% oxygen has nearly the same viscosity as oxygen. The viscosity of oxygen is 0.020; that of the helium-oxygen mixture is nearly 0.019. Their densities, however, differ; oxygen M.W. 32, helium is 4. Inasmuch as flow rates through orifices depend on density and vary inversely as the square roots of the molecular weight $(\sqrt{M.W.O_2}/\sqrt{M.W.He})$ under comparable circumstances, nearly three times the volume of the helium-oxygen mixture would pass through an orifice of unit size in a unit period of time as would oxygen $(\sqrt{32}/\sqrt{4})$.

Fixed Orifice Type of Flowmeters

The pressure difference between the two sides of the orifice increases as additional gas passes from the reservoir. The flow rate is proportional to the square root of the pressure difference. To illustrate: a unit volume of gas flowing through an orifice of unit diameter develops a pressure difference of one unit. The flow is then increased so that a fourfold increase in pressure difference develops. The flow rate, if measured, is found to be $\sqrt{4}$, that is, 2 units (Fig. 26.2). If the flow is such that a sixteen fold pressure difference develops the volume delivered is $\sqrt{16}$ or 4 units. The pressure differences which develop when gases of dissimilar densities flow through an orifice of a fixed diameter at identical rates vary with the density. The lighter gas develops the lesser pressure other things being equal. In comparing the

volumes delivered of two gases, one lighter than the other, the pressure differences vary inversely as the square roots of the densities of the gases. To illustrate: one unit volume of oxygen (M.W. 32) flowing through an orifice of unit diameter creates a pressure difference 4 times that created by a unit volume of hydrogen (M.W. 2) flowing under comparable circumstances, since oxygen is 16 times denser than hydrogen ($\sqrt{16}$ = 4). The flow rate of hydrogen at the same pressure difference through the same sized orifice would be twice that of oxygen (Fig. 27.2). The less the density of a gas, the smaller the orifice necessary to permit passage of a unit flow rate per unit of time. The flow rate is proportional to the diameter of the orifice. At a constant unvarying pressure differ-
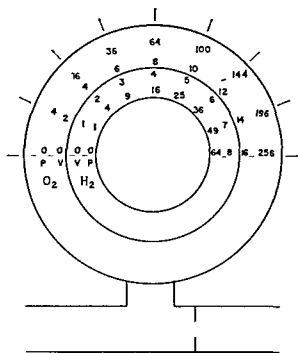
FIG. 27.2. Two gases of unlike densities flowing at a constant rate through an orifice of unit size develop pressure differences which vary inversely as the square roots of their densities.

ence the flow rate is proportional to the square of the diameter of the orifice. A large orifice is necessary in constructing flowmeters which measure high flow rates; a small one for low flow rates.

Variable Orifice Type Flowmeters

The variable orifice type of flowmeter consists of an elongated, usually transparent tube whose lumen tapers and exactly accommodates a spherical body, known as a "float," at its narrowest portion. The tube is arranged vertically with the widest portion uppermost. The gas is admitted at the lowermost portion and conducted away to the inhaler from the top. When no gas is flowing the float rests at the bottom of the tube. When gas first enters the tube enough pressure must develop to overcome the weight of the float and raise it off the bottom. A pressure difference develops between

FIG. 26.2. The rate of flow of a gas through an orifice is proportional to the square root of the pressure proximal (upstream) to the orifice.
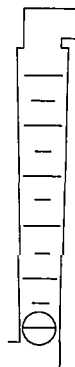
ORIFICE DIA.	PRESSURE DIFF.	VOLUME DEL.
16	1	256
8	1	64
4	1	16
2	1	4
1	1	1

Fig. 28.2. The flow rate of a fluid through a variable orifice varies inversely as the diameter of the orifice provided the pressure difference between the two sides of the orifice remains constant.

the bottom and top of the sphere causing it to rise in the tube and be suspended on a cushion of gas. The space between the float and the walls of the tube increases in size as the gas flow increases and the float rises higher in the taper. The float ceases to rise when the pressure on the underside is sufficient to balance the effects of gravity upon the float (Fig. 29.2). This elevation of the float in the tube causes an increase in the cross-sectional area of the space between the float and the tube and causes the pressure to fall (Fig. 29.2). Thus, as each adjustment in flow is made, the pressure on the underside of the sphere is readjusted to that value necessary to keep the float suspended. Since the cross-sectional area of the space between the walls of the tube and the float varies with the position of the float, the term variable orifice is used to designate this type of unit. The pressure difference between the top and bottom necessary to

keep a float suspended is the same, for a given float, at any position in the tube. The pressure, therefore, remains constant when the flow is varied and adjusted to the equilibrium point. For this reason, these flowmeters are often called *constant pressure* flowmeters. The widest

Fig. 29.2. The pressure between the top and the bottom of the float of a variable orifice flow meter after equilibrium is attained following changes in flow rate, is a constant at any portion of a tapered tube.

1 UNIT

1 UNIT
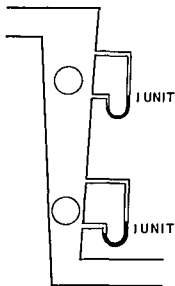
Fig. 30.2. A spherical float creates an orifice whose thickness is a circumferential line corresponding to its equator. Theoretically the clearance between the sphere and the tube is a true orifice. A cylindrical float creates a tubular opening (shaded area).
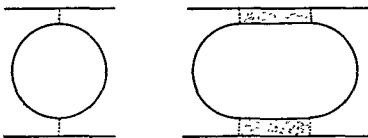
portion of a spherical float is the circumferential line which corresponds to the equator of the sphere. The width of this line is relatively insignificant. The clearance between it and the sides of the tube theoretically constitutes a true orifice. Actually some turbulence enters into the picture at this zone (Fig. 30.2).

The float need not be spherical. In some flowmeters the float is cylindrical, conical or in the form of a disk. The form, weight, and the size of the float and the angle of inclination of the taper of the tube are factors which determine the accuracy and performance of this type of flowmeter. Inasmuch as the pressure difference in a variable orifice flowmeter is equal to the pressure of the gases on either side of the float plus that necessary to suspend the float in the tube, it is obvious that the heavier the float the greater the pressure difference necessary to suspend the float and the less sensitive the instrument. These factors are discussed further on.

When the diameter of an orifice is varied in the manner which has just been described and the pressure difference remains constant, the flow rate of a gas varies as the square of the diameter of the orifice (Fig. 29.2). To illustrate: Suppose an orifice of one unit diameter admits a gas at a flow rate of one unit volume per unit time when the pressure difference on one side of the orifice is one unit. If the diameter is increased twofold with no change in pressure dif-

ference a fourfold increase in flow rate results (Fig. 29.2). Quadrupling the diameter, with the pressure difference remaining constant, causes a sixteen fold increase in flow rate.

Effects of Impedance to Flow on Flow Rate

Flowmeters are calibrated to discharge *into space without impedance.* Usually they discharge into a space containing a gas close to normal atmospheric pressure, that is, at 760 mm. Hg and room temperature (25°C.). The figures on the scale indicate the volume the gas will occupy at normal atmospheric pressure and room temperature. Scales of flowmeters used above or below atmospheric pressure require revision and correction. Flowmeters designed to be used when resistance to flow is present in the line are called *pressure compensated flowmeters.* These are discussed later.

Although the foregoing discussion has been concerned with ideal situations, it must be remembered that it is virtually impossible to construct an ideal orifice. In many devices the constriction is in the form of a narrow tube rather than a true orifice. Under these circumstances viscosity, in addition to density, plays a role in altering flow rates. These factors are discussed subsequently.

Individual Types of Flowmeters Used for Anesthesiology

There are as many designs of flow-
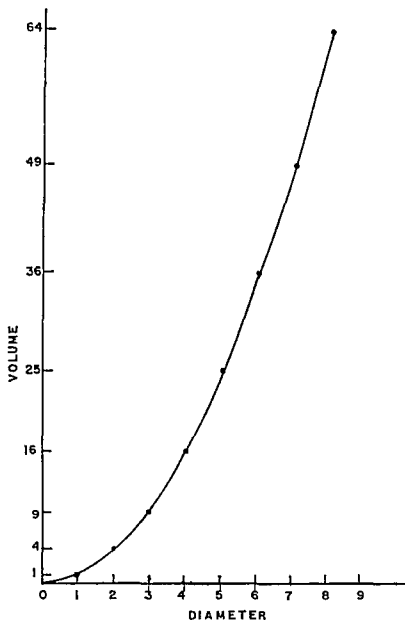
Fig. 31.2. The flow rate of a fluid varies as the square of the diameter of the orifice *if the pressure propelling the fluid remains constant.*

meters as there are manufacturers of anesthesia apparatus. Such terms as hydraulic flowmeters, dry flowmeters, rotameters, bobbin type flowmeters, gauge type flowmeters and so on have been introduced to describe the currently used units. Many anesthesiologists refer to the type of flowmeter by the name of the manufacturer. Basically, even though flowmeters differ in details of construction, they all embody either the principle of the fixed orifice or the variable (inconstant) orifice.

HYDRAULIC (CONSTANT ORIFICE) FLOWMETERS

Inside Flowmeters

The terms "hydraulic," "wet flowmeter" or "aquameter" are applied to a type of flowmeter introduced and supplied by Foregger. This is a fixed orifice type of device which employs a water manometer to measure the pressure developed by a gas as it passes through an orifice. The design known as the *"inside flowmeter"* consists of a slender, elon-
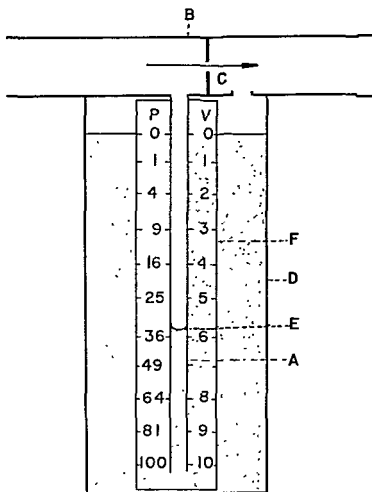
Fig. 32.2. Schematic representation of an inside flowmeter. The glass tube (A) is placed vertically at right angles to the delivery tube (B) and proximal to the orifice (C). The tube is immersed in water in a transparent container (D). The flow of a gas through (B) causes a rise in pressure in the area proximal to the orifice and forces the meniscus (E) downward. The flow rate (V) on scale (F) varies as the square root of the pressure difference (P) in the upstream and downstream portion of the tube.

gated glass tube placed at right angles to the delivery tube proximal to the orifice and on the side of the gas supply (Fig. 32.2). The glass tube, open at the bottom, is immersed in a sealed jar of water. The top of the jar and the section of the tube distal to the orifice which receives the gas communicate with each other. Thus, the pressure over the surface of the water in the jar equals that in the distal side of the orifice. The variations in pressure proximal to the orifice caused by the gas flow are transmitted to the column of water in the glass tube. A depression of the meniscus results in proportion to the flow rate. Actually, the tube attached to the side nearest the gas supply proximal to the orifice, together with the jar, performs the function of the conventional U type manometer (Fig. 33.2). Should the flow rate be greater than the maximum reading on the scale, the excess gas will bubble from the mouth of the tube through the water into the downstream portion of the delivery tube distal to the orifice. The units of pressure difference are translated into terms of units of volume flow. Calibrations are etched on the tube or a scale is placed directly behind the tube in the jar. Since flow rate is proportional to the square root of the pressure difference, assuming that one unit of pressure difference equals one unit of volume flow, 4 units of pressure difference equals 2 units of volume flow, 16 units of pressure difference equals 4 units of volume flow, 64 units of pres-
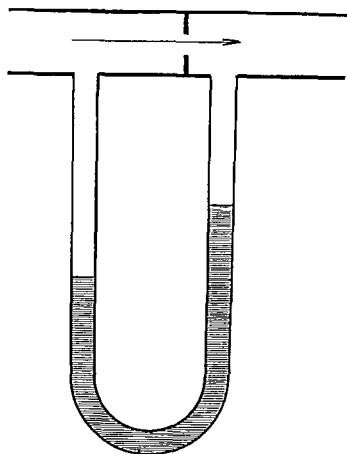
Fig. 33.2. The tube in the jar (Fig. 32.2) functions in the same manner as a U type manometer.

sure equals 8 units of volume flow and so on (Fig. 32.2). The notations on the scale are spaced farther apart at the high flow rate end of the manometer and are spaced close together at the low flow rate end. The readings, therefore, are made with less accuracy at low flow rates than at high flow rates. Since several gases are used, a number of individual flowmeters are arranged together in a single jar depending upon the number and type of gases the apparatus is designed to deliver (Fig. 34.2). The gases all pass into one common chamber or "head" in which they mix and from which they are distributed via a tube to the inhaler.

This type of flowmeter is calibrated empirically since it is the only manner in which discrepancies due to viscosity,

turbulence, friction, room temperature and other factors can be eliminated and accuracy assured. The scales for gases, such as oxygen, nitrous oxide and ethylene, which are used at high flow rates, are calibrated in liters per minute. Scales for gases which are used in lesser quantities, such as cyclopropane and "metabolic" oxygen, are calibrated in cubic centimeters per minute. The size of the orifice differs for each gas. The denser the gas, the wider the orifice must be for a particular flow rate. Two flowmeters are usually provided for oxygen, one for high flow rates and one for low. These are often referred to as "the coarse oxygen" and the "fine." The size of the orifice for the meter (fine) intended for the low flow rate, obviously, is smaller than that for the coarse.

Fig. 34.2. The inside flowmeter. Typical inside "hydraulic" flow meter designed to measure the flow rate of several gases simultaneously. The gases are collected into a common mixing chamber at the top of the jar and delivered to the apparatus.

Fig. 35.2. Outside flowmeter. Schematic diagram illustrating the principle of the outside hydraulic flowmeter. The gas is delivered into (A) the outlet tube through the orifice (B) and thence to the inhaler through (C). As the flow increases the pressure over the water in (A) exceeds that over (D) and causes a depression of the column (E). The greater the flow rate, the greater the pressure which develops and the greater the depression of the meniscus.

Outside Flowmeters

Similar in principle to the inside flowmeter, but different in design is the so-called *outside flowmeter*. This is basically a U type manometer (Figs. 35.2, 36.2). One limb is mounted on a scale upon which are engraved the calibrations of pressure difference translated in terms of volume per minute. This limb communicates with the portion of the delivery tube proximal to the orifice. The other limb of the U communicates with the portion of the delivery tube distal to the orifice. As is the case with the inside flowmeter, one such flowmeter is necessary for each gas All the gases from each individual meter ultimately flow into a common mixing chamber from which they are conducted through a delivery tube into the apparatus.

Fixed orifice types of flowmeters using water manometers can be made to have a high degree of accuracy and constancy of performance. The orifice, however, must be clean, free of debris and corro-
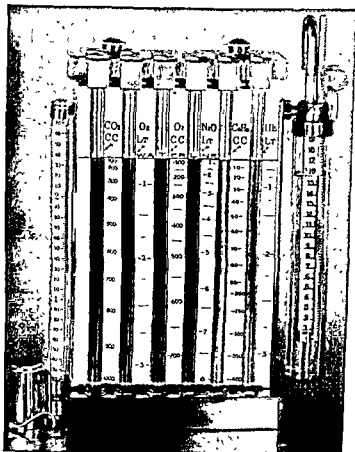
Fig. 36.2. The outside flowmeter. (Courtesy of Richard Foregger.)

sion, otherwise, the flow rates may be less than the calibration on the scale.

Gauge Type Manometers

Instead of a manometer a sensitive Bourdon type gauge may be used to measure the pressure difference in the fixed orifice type of meter. The units of pressure are translated in terms of flow rates (Figs. 26.2, 27.2). The underlying principle is identical to that used for "hydraulic" flowmeters. The Bourdon type gauge is not satisfactory for low flow rates if these gas volumes are to be accurately measured. It is widely used for oxygen therapy where flow rates range from 1 to 15 liters per minute and accuracy at low flow rates is not needed. Gauges of this type designed to measure

flows at fractions of a liter per minute tend to become inaccurate with time. The orifices, as in the case of hydraulic flowmeters, tend to become occluded with debris or the metal corrodes which, likewise, reduces their efficiency.

"Sight Feed" Hydraulic Flowmeter

With one exception, all "wet type" flowmeters are based upon the constant orifice principle. This exception is a hydraulic or "wet type" flowmeter, introduced by Foregger, known as the "sight feed" flowmeter. It was one of the earliest of the flowmeters used for clinical anesthesia. It consists of a slender, metal tube perforated at regular intervals along its length (Fig. 38.2). The upper end communicates directly with the source

of gas. The perforated portion of the tube is immersed vertically in an elongated, transparent wide mouth tube containing water. The flow of gas depresses the meniscus to the first perforation in the tube. The gas bubbles from it into the delivery tube. As the flow rate is increased the meniscus is depressed further and activates additional perforations. Thus the number of perforations activated is an index of the flow rate. The cross-sectional area of the orifice increases progressively as each successive perforation is activated. The size of the orifice equals the sum of the areas of all the activated perforations. The pressure remains constant. The number of perforations which are bubbling is an index of the flow rate. Several tubes may be assembled in one container when more than one gas is used. The gases are conducted to the inhaler through an exit tube at the top of the jar. Obviously, the finer gradations of flow rate are impossible to obtain with this type of meter. Each meter must be calibrated empirically for the particular gas which is to be measured. This

FIG. 38.2. Schematic diagram of the "sight feed" flowmeter. As the flow rate of the gas delivered through (A) is increased the meniscus is depressed in the perforated tube (B) immersed in jar of water (C). The gas escapes through the perforations into the outlet tubes (D) leading to the apparatus. The meniscus is depressed in proportion to the flow rate. As the flow rate is increased successive perforations are activated in proportion to the volume delivered.

meter is almost obsolete and little used in present day practice.

"Bobbin" Type Flowmeter

A "dry type" of flowmeter, sometimes referred to as the "bobbin," operates basically in the same fashion as the "sight feed" flowmeter. The better known of these is the Coxeter used by British anesthetists. This meter consists of a vertically placed transparent tube of uniform bore with a series of perfora-

FIG. 37.2. Cross section of gauge type of flowmeter. The gases enter tube (A) and pass through the orifice (B) to delivery tube (C). A difference in pressure develops between (A) and (C) which is transmitted to the diaphragm (D) which operates a clockwork mechanism. The gas flow is indicated on the dial calibrated in liters or fraction of a liter per minute.
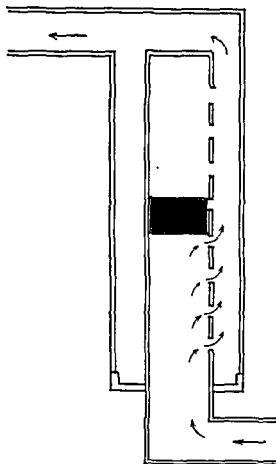
FIG. 39 2. The bobbin type of "sight feed" flowmeter employs the variable orifice principle The incoming gas forces the bobbin upward into the tube. The gas then escapes from the perforations at intervals spaced in proportion to the flow rate. As the flow rate increases the bobbin is forced further in the tube to activate additional perforations.

tions at regular intervals throughout its length (Fig. 39 2). A cylindrical float (bobbin) is accommodated snugly in the lumen to prevent the gas from passing around it. The bobbin must fit loosely enough for it to glide up and down the tube without resistance. The gas is admitted at the lower end; the upper end is sealed. As the gas flows, the bobbin rises in the tube and gas escapes from the perforations. The meter is enclosed in a transparent jacket into which the

gas from the perforations passes and from which it is conducted to the apparatus. The pressure in the tube adjusts itself to that which is necessary to sustain the weight of the bobbin in the tube. Calibrations of the rate flow are indicated at the level of each perforation. As the gas flow is increased the float rises higher and higher in the tube and the gas then escapes from an increasing number of perforations. Several meters may be assembled in a single encasement when more than one gas must be metered. The pressure in the tube remains constant but the cross-sectional area of the orifice varies with the number of activated perforations. Each flowmeter, as is the case with the hydraulic "sight feed" flowmeter, must be calibrated empirically for the flow of gas which it is intended to measure. The impedance caused by the friction between the wall of the tube, the float and the leakage around the float, particularly after the wear on the tube and float, reduces the accuracy considerably. The rate of flow increases in a stepwise fashion. The finer gradations of flow rates are not obtained with either the hydraulic "sight feed" or "bobbin type" flowmeters.

DRY TYPE—VARIABLE ORIFICE FLOWMETERS

The majority of variable orifice flowmeters in use consist of a spherical float in a vertically arranged transparent tube whose lumen is tapered with the widest portion uppermost (Fig 40.2). The float is supported by the gas flowing through the tube. Calibrations indicating the flow rate are usually etched on the tube or a scale behind it. The gases are admitted at the bottom and are conducted away from the top. In some flowmeters the tapered tube is encased in a larger,
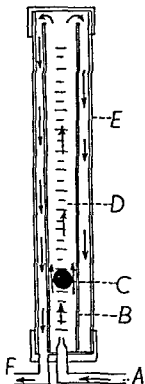
Fig. 40.2. Variable orifice type of flow-meter utilizing a spherical float in a tapered tube. Gas enters at nozzle (A) tapered tube (B) around float (C) and passes down tube (E) and into outlet tube (F).

to that of the length or diameter of the float. This is discussed later on.

The float is subject to wear because, at times, it unavoidably rubs along the wall of the tube. Both the shape and size of the float and the bore of the tube are altered by this wear which in due time introduces inaccuracies. By varying the length of the tube, the degree of the taper and the weight of the float, flow-meters may be constructed which measure gases at high or at low flow rates. Both features may be incorporated into a single flowmeter, if desired, by having an elongated narrow taper at the bottom and a widely flaring one at the top. Connell took advantage of this in his design of flowmeters.

The Connell Type

In certain flowmeters (Connell type) the tapered tube is inclined at an angle instead of being placed vertically. Two spheres are employed to prevent oscillation and to help the float stationary. These spheres roll up the incline in the tube as the gas is admitted at the bottom of the taper. They remain suspended at the point where the difference in pressure below and above the spheres is counterbalanced by their weight. The gas passes in front of the spheres instead of around them (Fig. 41.2). The size of the orifice is increased in the same basic manner as it is in the vertically placed

somewhat wider transparent compartment into which the gas passes and from which it is conducted to the apparatus. The float is made of stainless steel or other durable substance. Lightness is an asset. The heavier the float, the less accurate and less sensitive the meter. Flowmeters used for oxygen therapy (Thorpe tube) and for anesthesia apparatus (the E & J and most other apparatus) are usually of this design. Whether or not viscosity plays a role in the passage of gases through this type of flowmeter depends upon the relationship of the length of the narrow portion of the taper

Fig. 41.2. A variable orifice (Connell) type of flowmeter. The tapered tube (A) is inclined at an angle so that two spherical floats (B) slide up and down the inclined plane (C). The gas escapes through the space between the floats and uppermost part of the tube.
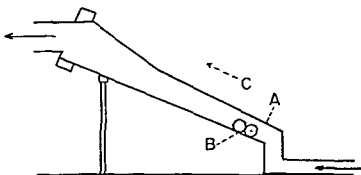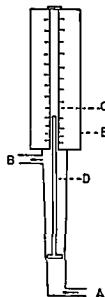
FIG. 42.2. Disk type (Heidbrink) variable orifice flowmeter. The gases from the supply tube (A) enter into the tapered tube and cause the plunger (D) to be forced into the tube (C). The gas flows around the edge of the disk. Stem (D) is pushed further into the transparent tube (C) along scale (E) as the flow rate increases.

tapered tube. The lower portion of the tube tapers gradually over a distance of several inches, thus permitting the measurement of gases at low flow rates with a fair degree of accuracy. In the upper portion the lumen flares out widely over a short distance, permitting the measurement of gases at high flow rates.

Disk Type Floats

Instead of a sphere, the float of certain variable orifice type flowmeters (Heidbrink) consists of a thin, horizontally placed disk which glides up and down a vertically placed metal tapered tube. The basic principle is essentially the same as described in the previous paragraph for the Thorpe tube. The tube is approximately three inches long, that is, it is much shorter than usual. The metal disk is attached perpendicularly to a thin stem which glides in and out of a transparent tube behind which is fixed a scale calibrated in units of flow rate (Figs. 42.2, 43.2). The gas enters at the bottom of the taper and is conducted to the apparatus from the top. The weight of the disk varies with the nature of the

gas used. As the gas is admitted the disk is elevated into the tube until the pressure is sufficient to sustain its weight together with that of the stem. The flow rate is indicated by the position of the top of the stem as it passes in and out of the glass tube. The disk is in the metal portion of the tapered tube and, therefore, not visible. Density and viscosity both play a role in measuring flow rates with this type flowmeter. Viscosity plays a role at low flow rates because the thickness of the disk creates a tubular passage at the narrow portion of the tube. At high flow rates, when the disk is in the wide section of the taper, the cross sectional area through which the gas passes is greater and the influence of the thickness of the disk is minimized. The opening then may be considered orificial instead of tubular. Density then plays the greater role and viscosity very little.

The Inverted Tapered Float

A tapered tube may be made to serve as both the orifice and the float. Flowmeters constructed on this principle (McKesson) are composed of light metal
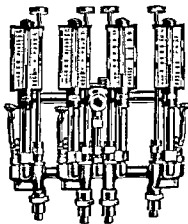
FIG 43.2. Flowmeters (Heidbrink) using the principle depicted in drawing in Figure 42.2.

FIG. 44.2. The "inverted taper" (McKesson) variable orifice type of flowmeter. The gas is admitted through the nozzle (A) into tapered tube (D) which *passes into calibrated* transparent tube of uniform bore (C) and are conducted to apparatus through tube (B). The tube (D) rises and falls in (C) in proportion to the flow rate.
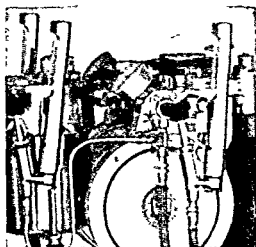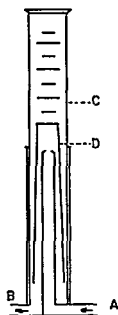
FIG. 45.2. Flowmeter utilizing the "inverted taper" (McKesson).

tapered tubes 4–5 inches in length, sealed at the narrow end. These are inverted vertically over a tube of nearly equal length to the tapered tube but slightly less in diameter than the narrowest portion of the taper (Figs. 44.2, 45.2). The inner tube is of uniform diameter. The gases are admitted through the inner tube and pass downward along the tapered tube. The tapered tube is encased in a transparent compartment *which acts both as jacket and as a collecting chamber for the gases flowing through the orifice. The gases are collected and conducted to the apparatus. The height to which the tapered tube rises in the transparent compartment is proportional to the flow of gas. The compartment is calibrated in units of volume flow rate. Obviously the tapered tube must be light, otherwise all semblance of sensitivity is sacrificed. Basically, the principles involved are the same as those in other variable orifice flowmeters. The higher the tube rises in the glass case the wider the orifice through which the gas flows.

THE ROTAMETER

The construction of the rotometer is based on the same general principles embodied in other variable orifice flowmeters. However, there are certain modifications and refinements which increase the accuracy and usefulness of the meter. Once again, an elongated, vertically placed tube with a tapering bore is used. The widest portion, again, is placed uppermost. The tube is considerably longer *than that used in the other flowmeters* of similar type. The float is cylindrical *with its lowermost portion tapering into* a point (Figs. 46.2, 47.2). An additional feature, in certain designs, is a "head" on the float which has a diameter somewhat greater than the body. The float is specially constructed of aluminum or other light, durable substance. A number of grooves are cut at an angle in the head or body of the float. These act like the blades of a turbine and cause it to spin in a rotary fashion. The gas enters the tube at the lowermost portion and supports the float in the same manner as it does the float of other flowmeters. In

addition, as the gas passes between the wall of the tube and the body of the float, some of it moves through the grooves. Since these grooves are cut at an angle the float is given a rotary thrust and set in motion on its vertical axis. The tube must be mounted in an absolutely vertical position; otherwise, the meter
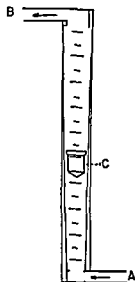
FIG 46 2. Rotameter type of flowmeter. Light plastic rotating bobbin (C) is suspended in transparent tapered tube Stream of gas enters at (A) and leaves at (B).

ERRORS IN MEASUREMENT OF VOLUMES DUE TO INTERCHANGING OF GASES AND FLOWMETERS

Discrepancies occur when gases are interchanged and flowmeters designed to measure volumes of one gas are used for another. Interchanging gases without recalibration of flowmeters is permissible
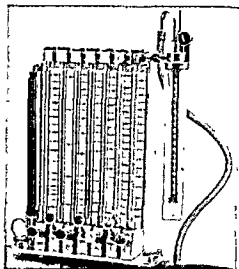
FIG. 47.2. A battery of rotameters. The gases pass into a common mixing chamber at the top from which they pass into the inhaler. (Courtesy of Richard Foregger.)

does not function properly. The rotation of the float reduces the possibility of contact with the wall of the tube by centering it. The errors due to friction and wear of the tube and float are, thereby, minimized. The rotameter has the advantage of being more accurate and allowing the measurement of gas volumes at low flow rates with a greater degree of accuracy. At low flow rates, viscosity plays a role to some extent in the rotameter. At high flow rates density plays the more important role. This is discussed further on in this chapter.

only when the gases have identical densities and viscosities. There are no situations in anesthesiology in which this requirement can be met. Two dissimilar gases may be measured on the same flowmeter when the constriction in the flowmeter is a true orifice. Thus carbon dioxide and cyclopropane, which have similar densities, may be measured on flowmeters calibrated for one or the other of these gases. However, the constriction in a fixed orifice flowmeter may not always be a true orifice. In some cases it is elongated, and is, in reality, a

capillary tube. In such situations errors arise due to viscosity of the gas if this point is not taken into consideration. In some flowmeters the opening may not be strictly orificial but the length of the constriction is relatively short and the effects of viscosity are negligible and may be disregarded.

In the variable orifice flowmeters at high flow rates the float is in the widest section of the tapered tube. The cross sectional area of the clearance between the float and the lumen of the tube, if this area were represented as a circle, would have a diameter which exceeds the thickness or length of the float (Fig. 48.2). The opening through which the gas clears can be considered an orifice. In this area, then, density would be the determining factor in the flow of gases. Viscosity plays a negligible role. At low flow rates the float is in the narrow portion of the tube. The cross sectional area

Fic. 48.2. A cylindrical float with appreciable length in a tapered tube acts as a "true" orifice at the widest portions of the taper, since its length is less than the diameter of the cross sectional area. In the narrow portion the passage way becomes tubular because the length exceeds the diameter.

of the space between the inside of the tube and the float is relatively less. The length or thickness of the float may exceed, appreciably, the cross sectional area. The space between the float and the tube, then, would be tubular rather than orificial. In the rotameter employing a cylindrical float, the cross sectional area cleared by the gas is represented by a circle and the diameter of this orifice would be less than the length of the body of the float. A gas, therefore, acts as though it were passing through a narrow tube in this part of the flowmeter. Viscosity would then become a major factor in the flow under such circumstances. Thus, if the flow rates of two gases of similar density but dissimilar viscosities are measured using the same flowmeter where this situation exists, a marked discrepancy in volumes would occur at low flow rates. Cyclopropane, which has a viscosity of 0.008, cannot be metered at low flow rates by a flowmeter of this sort which is designed to dispense carbon dioxide. Although the densities of both gases are nearly equal, carbon dioxide has a viscosity of 0.015. On the other hand, a mixture of helium and oxygen may be measured at a low flow rate on such a flowmeter calibrated for oxygen because the viscosities are similar. At high flow rates, however, the flow is no longer comparable. The opening is a true orifice. At high flow rates a marked discrepancy in volumes metered occurs because the density of the mixture is nearly one-third the density of oxygen.

When a sphere is used for a float the space between the tube and the equator of the sphere represents a true orifice because the float has no appreciable length (Fig. 30.2). Viscosity does not play a role in this type flowmeter. Unless

one is thoroughly familiar with the construction of a flowmeter, it is a good policy to calibrate it if it is used for a gas other than the one for which it was intended.

CALIBRATION OF FLOWMETERS

Flowmeters may be calibrated by the water displacement technique. This does not require any elaborate apparatus. Any calibrated buret, graduate or measuring bottle may be used. When calibrating a flowmeter designed to deliver small volumes at low flow rates, a container of a liter capacity is satisfactory. The container is filled with water and inverted into a wide pan partly filled with water so that its mouth is completely submerged. A tube which conducts the gas from the flowmeter is placed in the mouth of the container beneath the surface of the water in the pan. The time *required to displace a given volume of* water by the gas is determined.

One may also employ spirometers of the type used for basal metabolism determinations, a breathing bag or some such device which measures gas volumes accurately.

PRESSURE COMPENSATED FLOWMETERS

The calibrations on a flowmeter indicate the volume the gas will occupy when allowed to expand to normal atmospheric pressure at room temperature. A restriction placed at the outlet of a flowmeter causes a pressure to build up behind the restriction. Humidifiers, nebulizers, jets, and other restrictive devices introduce such a *back* pressure. The flow of gas, when this happens, is *not the calibrated value* on the gauge. In the variable orifice type flowmeter, the flow is greater than the indicated value. A restriction placed in the fixed orifice

type of flowmeter will cause a large flow to be indicated when actually it is far less or none if there is complete occlusion at the outlet. Ordinarily, flowmeters are designed to indicate flow rate only when the gas is discharged into a space in which the gas will be at or near atmospheric pressure. When the discharge is into an area in which there is restriction to the flow, a pressure compensating arrangement is necessary to obtain accurately metered flow rates. The variable orifice type flowmeter may be adjusted to compensate for restrictions interposed between the outlet and the atmosphere. The fixed orifice type, unfortunately, may not.

Gas is admitted to the ordinary flowmeters from the supply source through a controllable needle valve which is located proximal to the tapered tube (Fig. 49.2).
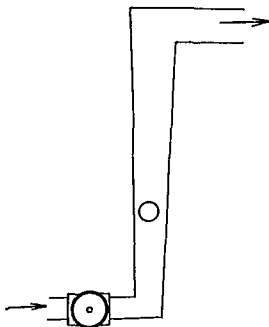
FIG. 49 2. Flow meter which is uncompensated for pressure. The *control valve is placed proximal to the orifice.* Obstructions at outlet restrict flow which results in false values for calibrated rates.

The gas pressure is reduced to atmospheric pressure in the tapered tube. In the pressure compensated flowmeter the needle valve is placed distally—between the tapered tube and the outlet. The *pressure in the tapered tube is the same as in the supply line*. The flow is controlled by the needle valve and is reduced to atmospheric pressure *after* it has passed through the tapered tube (Fig. 50.2). The flowmeter is calibrated in terms of the number of liters the gas will occupy after it expands when discharged to atmospheric pressure. If no restriction is attached to the outlet of a pressure compensated flowmeter, the reduction to atmospheric pressure occurs immediately upon discharge. If a restriction, as for example, a nebulizer, is placed beyond the needle valve, the discharge to atmospheric pressure occurs after the gas passes through the nebulizer. Adding the restriction to the discharging gas has the same effect as turning down the needle valve. In other words, the restriction decreases the flow but has no effect on the accuracy of the indicated flow. Thus, a pressure compensated flowmeter may be used whether or not a flow restrictive device is attached to the flowmeter. The tapered tube, however, must be calibrated for a given inlet pressure. Usually this pressure is 50 lbs. per sq. in. The pressure of the gas delivered from the supply source (regulator) to the outlet tube must be maintained at or as close as possible to the pressure for which the calibrations were made, otherwise errors will be introduced and the indicated flow will differ from the actual.

NEEDLE VALVES

The flow of gas from the storage cylinder is controlled by valves often referred to as *needle or pin valves*. A needle valve
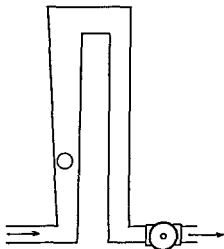
FIG. 50.2. Pressure compensated flow meter. The control valve is placed distal to the orifice. Obstructions at the outlet do not influence flow meter readings.

is composed of a slender metal rod or pin tapered at one end which screws into a cylindrical opening in a metal block by means of fine threads. The number of threads per unit length are so numerous that one complete turn causes the pin to advance a very short distance. The tapered end fits into a recess at the bottom of the opening which is referred to as the seat (Fig. 51.2). The point of the pin fits snugly in the seat. By turning the pin so that it screws outward, the snugness of the contact with the seat may be varied. An opening in the bottom of the seat admits the gas which escapes around the tip of the pin along the shaft where it finds its way into another opening further up in the block and outward to the flowmeter. Thus, a minute "leak" whose size can be varied is created from the gas supply to the inhaler. As the pressure in the supply cylinder declines the pin must be moved outward to create a larger "leak" to compensate for this pressure decrease. A hazardous situation is often created in the types of apparatus which are arranged so that
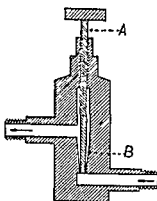
FIG. 51.2. Cross section of a pin valve. The valve is interposed between a point of high pressure and the atmosphere. It permits control of flow rate of gas from a high pressure system to a low pressure system without using a reducing valve. It acts both as a flow control and as a reducing valve.

the needle valve is interposed between a high pressure gas supply and the flowmeter. When an exhausted cylinder is replaced by a full one, an excessively high pressure may be transmitted suddenly to the flowmeter should the main cylinder valve be opened without first turning down the needle valve. In order to avoid this, a special valve called a *pressure reducing valve* may be interposed between the gas supply and the needle valve. This permits the withdrawal of gases from a low pressure system. The hazard of transmitting an excessively high pressure to the flowmeter is eliminated by the use of the reducing valve. In addition, coarse needle valves may be used instead of fine ones when reducing valves are present. Needle valves for high pressure systems without reducing valves require fine threads so that the unseating which occurs with each turn of the pin is slight. Were this not the case it would be impossible to supply the gas at graded flow rates. Adjustments due to fall in pressure must be

made in both types of apparatus b fluctuations in flow rate are not as pr nounced in the low pressure systems.

REDUCING VALVES

Principles of Construction

A reducing valve is a gas pressure re ulator which permits the expansion of gas from a relatively high, but variabl pressure to an area of lower and mor constant pressure. The high pressur area is the storage cylinder. The valv consists of a chamber communicatin with the inlet from the cylinder bu which can be isolated from it by a sel sealing automatic valve. The pressure o the gas decreases in a stepwise manner Thus, a gas in a cylinder at a pressure o 2000 lbs. per sq. in. passes through valve into the chamber where the pres sure is 60 lbs. per sq. in. at which point the flow ceases. The gas may be drawn from this low pressure area into the flow meter through a needle valve. When no gas is being drawn through the needle valve the pressure in the small chamber is able to offset the larger pressure to close the valve communicating with the cylinder. Thus, a small pressure in one area balances one which is many times greater in another. This is accomplished in the following manner: Pressure is a force per unit area. The pressure of a fluid is transmitted equally in all directions. Assume two cylinders containing oxygen were available, one fully loaded and one partially loaded. Each square inch of the interior of a fully loaded cylinder of oxygen is acted upon by a force of 2000 lbs./ sq. in. at room temperature. Assume the pressure in the partly loaded cylinder is 200 lbs./sq. in. Assume this cylinder communicates with a piston whose diameter is 10 sq. in. The total pressure on the pis-
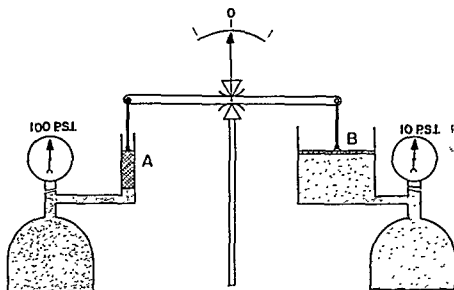
Fig. 52.2. Basic principle underlying construction of reducing valve. A pressure of small magnitude may balance one of larger magnitude by proportionately increasing the area over which the lesser acts. A pressure of 100 lbs. per sq. in. exerted on piston (A) having an area of one inch is counterbalanced by a pressure of 10 lbs. on piston (B) which has an area of 10 sq. inches. The total pressure on each piston is the same. The weights of the pistons are identical.

ton would be 2000 lbs. If this piston were allowed to oppose a second piston having an area of 1 sq. in. communicating with the fully loaded cylinder containing a gas at 2000 lbs./sq. in. (which would, therefore, be acted upon by a force of 2000 lbs./sq. in.) the two forces would balance each other (Fig. 52.2). The reducing valve operates on the same principle. One wall of the low pressure section consists of a distensible diaphragm whose area is much larger than the area of the seat of the valve controlling the flow from the cylinder outlet into the low pressure section. For example, assume that the area of the seat of the valve closing the pressure inlet is 1" (Fig. 53.2). The pressure of the gas in the cylinder is 1800 lbs./sq. in. The pressure on the 1" closing valve is 1800 lbs. The area of the diaphragm is 30 sq. in. Gas flows from the cylinder into the chamber and presses upon the dia-

phragm and exerts a pressure of 60 lbs. per sq. in. The total pressure on the diaphragm is 30 sq. in. × 60 lbs. per sq. in. or a total of 1800 lbs. The pressure on the surface of the 1" valve equals that of the diaphragm. Thus, a pressure of 60 lbs. is able to oppose a force or a valve seat 1" in diameter acted upon by a force of 1800 lbs./sq. in. The forward and backward excursions of the diaphragm operate a lever which controls the seating and unseating of the smaller valve which seals off the gas coming from the cylinder when the pressure is equalized, and allows it to open when the pressure falls below 60 lbs. A needle valve allows the gas to escape from the low pressure section, thereby reducing the pressure and the force on the diaphragm. This in turn causes the seat of the valve to the cylinder to be opened. When enough gas has been admitted to equalize the two forces the valve closes
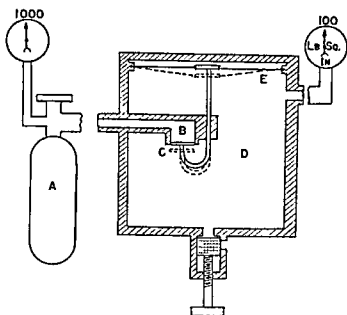
FIG. 53.2. Schematic representation of principle underlying the construction of a reducing valve. The pressure from gas supply (A) is exerted on the piston (B) which opens valve (C) and admits gas into chamber (D) which in turn exerts pressure on diaphragm (E). The area of diaphragm (E) is greater (in this case 10 times) than that of piston (B) in the outlet of the cylinder. Therefore, 1/100 of the pressure (the pressure in chamber (D)) balances that in the cylinder (A). Equalization of the pressures causes closure of valve (C). A decrease in pressure relaxes the diaphragm (dotted lines) (E) and causes the opening of valve at (C).
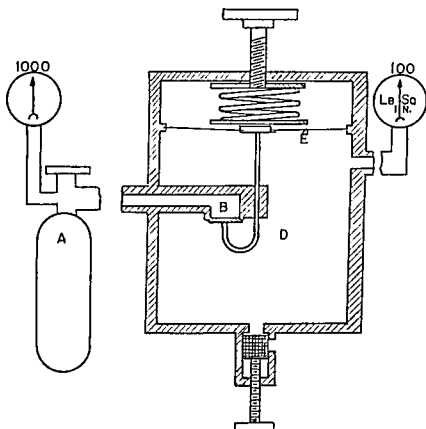
FIG. 54.2. Compensated reducing valve. As the gas is withdrawn from the supply the pressure declines. The balancing pressure on diaphragm (C) necessary for closure of valve (B) is reduced proportionately. The pressure in chamber (D) is maintained at fixed value by varying tension on spring (F) by turning the screw (G).
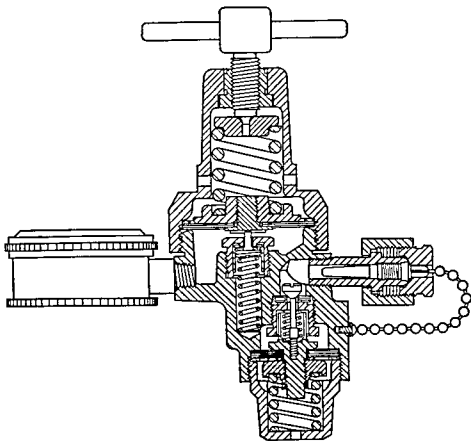
Fig. 55.2. Two stage regulator.

again and the gas flow ceases.

As the supply of gas in the storage cylinder is depleted the pressure in the cylinder declines. The pressure in the low pressure section necessary to balance the pressure in the cylinder is no longer 60 lbs. but decreases in proportion to the decrease in the cylinder pressure. At a 1500 lbs. cylinder pressure, for example, the pressure on the diaphragm necessary to oppose the cylinder pressure is 50 lbs./sq. in.

Flowmeters and other devices which operate at a fixed and unvarying pressure for proper performance must have some compensating mechanism to overcome this variation in pressure in the low pressure area caused by withdrawal of gases from the cylinder. This may be accomplished by counterbalancing

this decrease in force with an adjustable spring which presses in the outer surface of the diaphragm and increases its tension (Fig. 54.2). A pressure recording gauge must be present on such reducing valves in order that one may determine how much compensating tension must be applied with the spring. As the pressure in the cylinder decreases the tension on the diaphragm must be increased proportionately so that a constant pressure may be maintained on the low pressure section of the device.

Thus, reducing gauges are of two types, the *fixed pressure* type and the *adjustable or variable pressure*. In the fixed pressure type, variations due to cylinder pressure variations cannot be corrected. Pressure reducing valves are not necessary when gases dispensed at

low pressures, as for example, cyclopropane, are used. Their primary purpose is to reduce high pressures to safe operating pressures. Pressures ranging between 40 and 60 lbs. per sq. in. are relatively safe.

Regulators used for oxygen therapy cause the pressure to be reduced in stages in a stepwise fashion Fig. 55.2. Usually three stages are employed. In the first stage the pressure is reduced from 2000 lbs. per sq. in. to 750 lbs. per sq. in. The second stage causes a decrease to 400 lbs. per sq. in. and the third stage to 60 lbs. Single stage regulators reduce the pressure from 2000 lbs. to 60 lbs.; two stage regulators reduce the pressure from 2000 lbs. to 450 to 60 lbs. The single stage regulator has a relatively shorter life due to rupture of the diaphragm from repeated trauma to it.

Physics and Chemistry of Inhalational Appliances

REQUISITES OF INHALATIONAL DEVICES

THREE CONDITIONS must be fulfilled for satisfactory inhalational anesthesia: (1) the assurance of an adequate oxygen tension in the alveoli and blood; (2) the maintenance of the alveolar carbon dioxide tension within normal range; (3) the establishment and maintenance of an adequate tension of anesthetic drug in the alveoli and blood. Consequently all appliances for the administration of inhalational anesthesia, from the simplest to the most complex, have three essential features: (a) a source of oxygen which assures an adequate supply and satisfies the physiological requirements of the patient, (b) provisions for the elimination or absorption of carbon dioxide and (c) a device or devices for dispensing the volatile anesthetic. The latter consist of vaporizers for volatile liquids or meters for gaseous agents. Devices for the administration of gases and vapors are referred to as being open or closed. Closed devices are referred to as inhalers.

DEAD SPACE

Types

In designing appliances for inhalational purposes, whether they be for therapeutic gases or for volatile anesthetics, dead space is the utmost concern. Three categories of dead space are recognized: physiological, anatomical and mechanical. *Physiological dead space* is the space in the lungs ordinarily occupied by fresh air after inspiration. The gases in the physiological dead space do not participate in the interchange which goes on in the lungs, that is, they do not give up oxygen or take up carbon dioxide. *Anatomical dead space* is the space in the air passages down to the terminal bronchioles. It contains the gases which do not pass into the area lined with respiratory epithelium. *Mechanical dead space* is the space in an inhalational appliance occupied by exhaled gases which are rebreathed without change in composition. The rebreathed gas is neither freed of carbon dioxide nor is it replenished with oxygen or anesthetic gas or vapor. Anatomical and physiological dead space are not directly related to this discussion. Mechanical dead space is, however, and merits discussion (Fig. 1.3).

The method which affords the least dead space and the one which permits the least rebreathing is the one in which there is no enclosure over the face or nares. The ideal way to administer an inhalational gas or vapor and eliminate rebreathing entirely would be to place the patient in a large room filled with the mixture necessary to maintain anesthesia. This, obviously, would be impractical. Any enclosure which restricts movements of gases from the nose and mouth to outside fresh air causes some
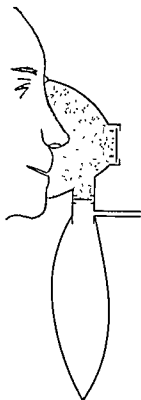
FIG. 1.3. Shaded area represents the mechanical dead space in a semi-closed inhaler of the nonrebreathing type. The valve separates inspired from noninspired gases.

degree of rebreathing and, therefore, creates dead space. The space from which rebreathing occurs should be as small as possible. All *mask* techniques are complicated by some degree of rebreathing.

TYPES OF INHALATIONAL METHODS

Gaseous and easily volatilized drugs may be administered by one of four inhalational methods: (1) the open vaporization (this is also referred to as the open cone or open drop technique), (2) the insufflation, (3) the semi-closed and (4) the closed or rebreathing. The physics and chemistry pertaining to each of these methods are important and merit discussion.

OPEN VAPORIZATION

PRINCIPLE

The open vaporization technique needs little description to most readers.

An easily volatilized liquid is vaporized by having a subject inhale through gauze or a similar absorbent saturated with a liquid. Ordinarily, a wire frame supports the absorbent and forms a mask which fits over the patient's nose and mouth. The liquid is dropped uniformly over the mask at a rate to maintain the necessary vapor tension in the inspired mixture. The vapor tension usually fluctuates widely due to numerous variable factors which are present. Among these are the rate and depth of respiration, the cooling of the gauze and supporting metal frame caused by evaporation of the drug, the influence of environmental temperature and the wetting of the gauze by condensation of the exhaled moisture.

TENSION DEVELOPED

Faulconer and his associates have studied the vaporization of ether, by the open method, in some detail. An appreciable fall in temperature results from vaporization of the liquid. The administration of open ether to a 70 kilogram adult breathing 20 times per minute at a tidal exchange of ½ liter at 25°C. causes the temperature of the mask to fall to a point somewhere between —2 and —8°C. The heat transfer necessary to continue vaporization at the rate necessary to maintain anesthesia may not be adequate and the process is retarded. At temperatures of 25°C. the theoretical vapor tension of ether is 400 mm. Hg. Using the open drop method, under the usual clinical conditions, the vapor tension varies between 35 to 150 mm. Hg, the average being 35 to 75 mm. Hg. The partial pressure of ether vapor may be increased by increasing the number of layers of gauze. Ordinarily six are used. When eight or ten layers are used, all

other factors being equal, the vapor tension beneath the mask increases. Other volatile liquids, such as chloroform, trichlorethylene, and vinyl ether behave in the same fashion as ether does. Qualitatively the situation is identical though quantitatively the individual tensions and temperatures differ.

SUB-OXYGENATION AND CARBON DIOXIDE RETENTION

Besides the inadequate and variable vapor tension, another serious drawback to the open methods is the dilution of the oxygen in the inhaled air by the vapor. This may be sufficient to cause an appreciable degree of anoxia. In clinical measurements in man, at sea level, a quantity of inspired ether exerting a tension of 100 mm. Hg causes the oxygen tension to fall from the usual of 152 mm. Hg to values as low as 120 mm. Hg. Anoxia from this cause may be corrected by insufflating a half liter or more of oxygen beneath the mask. Even though, in open methods, the flow of inspired and expired gases is not impeded, some rebreathing occurs and a slight, though insignificant, increase in inhaled carbon dioxide tension results. This is true when any mask, no matter how open or how small, is placed over a patient's face. Tensions of up to 25 mm. Hg may easily develop.

DRAWBACKS

Besides these forementioned objections there are other serious drawbacks to the open method. The vapor blown out of the mask during exhalation is wasted. Not only is the drug wasted but the evaporation of the additional unused ether contributes further to the undesirable cooling. Variations in tidal exchange cause fluctuations in concentra-

tion. As the rate and depth of respiration increase there is greater dilution of the vapor and the partial pressure decreases progressively. Another objection to open methods is that cold vapors are inhaled. Body heat is lost as a result. The fact that a fire hazard is created when flammable liquids are volatilized in the open method is obvious.

INSUFFLATION TECHNIQUE

PRINCIPLE

The insufflation technique, reduced to simplest terms of definition, is the forcing of a continuous stream of a mixture of gases and vapors under varying degrees of pressure into the nasopharynx, oropharynx or trachea. At high flow rates a positive pressure develops in the airway. Flow rates which cause pressures to exceed 25 to 30 mm. Hg may activate the stretch reflexes in the lungs and inhibit respiration and cause apnea. Ordinarily, this is no problem because flow rates exceeding 10 liters per minute are seldom used, and, at such flow rates, apnea does not ordinarily occur.

TENSION DEVELOPED

One noteworthy drawback to the insufflation technique is that the inspired gas tensions are subject to moment to moment variations during inspiration. During the inspiratory phase of respiration the rate of inflowing air or gas mixture into the lung accelerates from zero, when inspiration begins, to a maximal flow rate of 30 or more liters per minute at the point of maximum effort after which it once again declines to zero at the end of inspiration (Fig. 2.3). Obviously the maximum flow rate which develops at a given instant varies from person to person, since it depends upon

liters per minute and then decelerate to
zero at the inspiratory pause. The in-
sufflated gases in the upper air passages
are blown outward as the alveolar and
bronchial gases are expired. In infants,
children and small adults the tidal vol-
umes are, comparatively speaking, of
lesser magnitude than in adults. The di-
lutional factor is not as serious as it is in
adults. In adults, insufflation techniques
may not provide adequate flow rates to
maintain the gas and vapor tensions nec-
essary for anesthesia. This deficiency of

Fig 2.3. Moment to moment variations in
velocity of ambient gases during inspiration
and expiration plotted graphically result in a
sinusoidal type of curve. During the time in-
terval indicated by the shaded areas gases in-
sufflated at 10 liters per minute are diluted with
atmospheric air. During time interval (A) they
are undiluted During expiration insufflated
gases are forced out of respiratory passages

the respiratory effort, the minute volume
requirement and the size of the subject.
Let it be assumed, however, that a gas
mixture is insufflated at a flow rate of 10
liters per minute into the airway of a
subject whose maximum rate of inflow
during inspiration attains, at a given in-
stant, a flow rate of 30 liters per minute.
There will be an interval of time during
the inspiratory cycle during which the
flow rate being delivered by the appara-
tus is less than this and insufficient to
fully meet the inspiratory requirements
of the subject (Fig. 2.3). This deficiency
in flow rate is met by the air which is
drawn into the mouth and nose from the
outside atmosphere. This extraneous air
obviously dilutes the mixture being sup-
plied from the apparatus. In a like man-
ner, during expiration, the gases acceler-
ate from zero to a maximum of 30 or more

Fig. 3 3. Demand type valve. Inspiratory effort
in the tube (A) causes negative pressure to be
transmitted to diaphragm (B) which is relaxed
and activates valve (C). This permits gas in
chamber (D) to enter valve from feed line (E)
and to escape through opening (F). The outer
surface of the diaphragm is in contact with at-
mospheric air through opening (G)

the insufflation technique also applies to gases and vapors other than anesthetics. Dilution with air occurs, for example, when pure oxygen is administered by nasopharyngeal insufflation.

ADVANTAGES AND DISADVANTAGES

Sub-oxygenation during insufflation is readily obviated by using oxygen enriched atmospheres. The disposal of carbon dioxide is unhampered during intraoral and intranasal insufflation if there is no impedance to the airway. During intrachal insufflation, however, the lumen of the trachea is frequently, partially occluded by the delivery tube. Oxygenation may be adequate but carbon dioxide elimination may be hampered.

There is less rebreathing with the insufflation techniques than with any other inhalational method because the mechanical dead space is approximately zero. The insufflation techniques, however, are wasteful. Also, a fire hazard exists when flammable gases and vapors are used.

SEMI-CLOSED INHALERS

TYPES

Semi-closed and closed inhalers obviate, to a large extent, the foregoing objections to the open and insufflation technique. In the semi-closed inhalers there is a complete enclosure of the inspired atmosphere and dilution of the inhaled gases by air does not occur. A variety of semi-closed inhalers is available but they may all be resolved into either one of two basic types—those which permit rebreathing or recirculation of inhaled gases and those in which there is no recirculation. The latter type is often referred to as the *non-rebreathing* semi-closed inhaler. Strictly speaking, however, no inhaler is completely devoid of rebreathing. Some rebreathing occurs, as has been mentioned, when any mask, irrespective of the type, is applied to the face.

NON-REBREATHING TYPE

A semi-closed inhaler consists of a mask or a *face piece* connected to a reservoir, known as a breathing bag. The inhaler is supplied with an uninterrupted flow of a mixture of gases and vapors of constant composition. A valve interposed between the reservoir and the mask prevents recirculation and rebreathing of exhaled gases. Another valve, placed between the mask and the outside atmosphere, prevents the drawing of air into the inhaler and allows ejection of gases to the outside (Fig. 1.3). The valve between the mask and the breathing bag allows gases to pass into the mask only. Thus, a unidirectional flow is established from the reservoir into the lungs and from the lungs to the outside atmosphere. Ordinarily the capacity of the breathing bag is 8 to 10 times the tidal exchange of the subject. Obviously the prescribed gas mixture must be supplied at flow rates which meet the respiratory demand of the subject. This is accomplished by (1) supplying a continuous flow into the breathing bag or (2) by an intermittent flow from a demand valve.

Demand valves are devices, the construction of which is too complex for discussion here. A demand valve is activated by the negative pressure created during the inspiratory phase of the respiratory cycle (Fig. 3.3). A gas or a mixture of several gases is admitted into the inhaler from a high pressure reservoir through this valve. The flow continues as long as the negative pressure is being

corrugated tubes are interposed between the bag and mask. Each tube has a valve which establishes a unidirectional flow from mask to bag and bag to mask (Fig. 5.3). An exhalation valve is also placed on top of the mask or at the junction of the breathing bag to allow escape of excess gases. The To and Fro permits rebreathing of gases; the circle permits re-
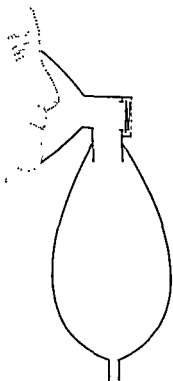
FIG. 4.3. To and Fro semi-closed inhaler. The exhalation valve at top of mask is spring loaded to restrict volume of expirations. Degree of rebreathing varies with the degree of restriction.

created and ceases as soon as inspiration is over and expiration commences.

The disposal of carbon dioxide from non-recirculating and demand type inhalers is adequate provided the valves function properly. The only carbon dioxide rebreathed is that in the dead space air of the mask. The amount rebreathed depends upon carbon dioxide output, the size of the face piece and the magnitude of the dead space.

REBREATHING TYPE

Omission of the valve between the mask and the breathing bag of a semi-closed inhaler permits rebreathing of gases contained in the fittings beyond the face piece. This is the *To and Fro semi-closed* inhaler (Fig. 4.3). A *circle type* of inhaler may be made also. Two

FIG. 5.3. Closed Circle inhaler may be converted to a semi-closed inhaler by placing an exhalation valve (H) in the system. The gases may be passed over the soda lime in the cannister (C and C₁) or bypassed into the bag. Fresh gases are admitted from inlet I.

FIG. 6.3. Gas mixtures whose composition is 4 to 1 part oxygen must be supplied *into* a semi-closed inhaler at the minute volume exchange required by the subject at a particular moment to maintain unvarying inhaled oxygen tensions. Curves indicate the rapidity of decline in inspired oxygen tension of a subject having a minute volume of eight liters per minute breathing from a semi-closed inhaler being supplied a gas mixture containing 21% oxygen at flow rates in liters per minute indicated by the figure in a circle. Mixtures used at low flow rates must contain more than 1 part oxygen to 4 of other gas or vapors.
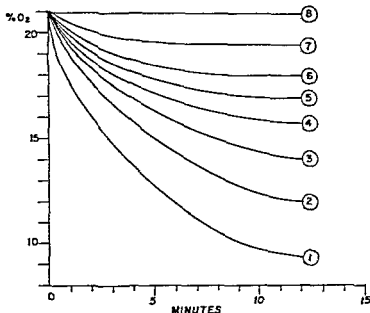
circulation which is tantamount to re-breathing. In both units, the gas mixture must be supplied at high flow rates to prevent accumulation of carbon dioxide and a fall in oxygen tension in the inspired gases. Adequate oxygen tensions and satisfactory carbon dioxide elimination are not possible unless the flow rates are equal to or greater than the minute volume exchange of the subject using the inhaler. Sub-oxygenation occurs even though the mixture being delivered into the inhaler contains 20% oxygen. In clinical trials, for example, in which a subject breathed from an inhaler to which air was supplied at a flow rate ¼ the minute volume exchange, beginning with 20% oxygen and 80% nitrogen in the mask, after 3 minutes, the concentration fell to less than 15%. The arterial blood oxygen saturation fell from 95 to 70%. At flow rates corresponding to ½ and ¾ the minute volume exchange of the subject the oxygen tensions increased proportionately but were still below the physiologic minimum (Fig. 6.3). Only when the flow rate was equal to or greater than the minute volume exchange of the sub-
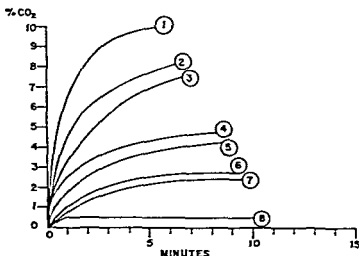
FIG. 7.3. Unless carbon dioxide is absorbed by chemicals, the tidal exchange of the subject must be ejected from a semi-closed inhaler to eliminate the excreted carbon dioxide. Curves indicate degree and rapidity of buildup of carbon dioxide tension at the lips when flow rates in liters per minute indicated by the figure in the circle are supplied to a semi-closed inhaler being used by a subject with an 8 liter minute volume.
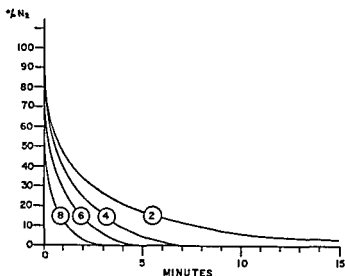
Fig. 8 3. Elimination of nitrogen from the lungs using pure oxygen as the washout gas in a semi-closed system requires approximately 2½ minutes in subjects with normal pulmonary function when the washout gas is supplied at the minute volume exchange of the subject. At flow rates less than the minute volume washout is delayed.

ject was the inhaled oxygen in the mask 20% Carbon dioxide rose from ½% to 7% within 15 minutes at flow rates equal to ¼ the minute volume exchange (Fig. 7.3).

In order to eliminate the carbon dioxide completely or to barely detectable levels flow rates exceeding the minute volume exchange are necessary. In a series of experiments the carbon dioxide returned to the mask at twice the minute volume exchange was 0.02%. The problem of adequate oxygenation and carbon dioxide elimination when using low flow rates can only be solved by enriching the mixture with oxygen and absorbing carbon dioxide with chemicals.

Semi-closed inhalers are necessary for anesthesia or inhalation therapy techniques requiring nitrogen "wash-out" from the lungs and tissues. Nitrous oxide, for example, is effective at high alveolar tensions which can only be attained by displacing the pulmonary nitrogen with the gas. In order to accomplish this the semi-closed inhaler is necessary. The "wash-out" gas, whether it be oxygen, ethylene, nitrous oxide or helium, must be delivered into the inhaler at the minute volume exchange of the subject to

accomplish a rapid "wash-out." In an average sized adult with normal pulmonary function the nitrogen is completely eliminated from the alveoli within 2½ minutes (Fig. 8.3). In pulmonary disturbances in which there is interference with effective gaseous exchange the nitrogen requires a longer time for elimination.

Variations in size and total capacity of the inhaler have little influence on the rate of "wash-out" provided the system is filled initially with the "wash-out" gas. Likewise, data concerning oxygenation and carbon dioxide elimination are little influenced by variations in size. The position of the exhalation valve, whether it be on the canister, bag holder or directly on the mask, has no appreciable influence on the "wash-out," oxygenation or carbon dioxide accumulation. Values are the same throughout. This applies to both the To and Fro inhaler and the circle arrangement. The length and capacity of the corrugated tubings in the circle arrangement and variations in size of breathing bag, likewise, make no difference. These principles are applicable to the administration of all gases,

whether they be air, oxygen, nitrogen, helium, nitrous oxide or ethylene.

CLOSED SYSTEM INHALERS

The closed system is designed to permit complete rebreathing of exhaled gases and vapors. A tight fitting face piece is necessary to assure a leakproof system. The metabolic requirement of oxygen and the necessary gaseous or vaporized drug are delivered into the inhaler as needed. Carbon dioxide is removed by chemical absorption. The closed system permits administration of anesthetic and therapeutic gases under pressure, highly enriched with oxygen. Enclosure of the gases reduces the fire hazard, eliminates waste of gases, and provides a steady inhaled vapor or gas tension of the anesthetic. Two types of inhalers are available—the To and Fro and the circle. In the To and Fro a canister containing a chemical absorbent usually soda lime is interposed between the mask and the breathing bag. In the circle system, the canister is at a distance from the mask separated by two corrugated breathing tubes. Valves at the inlet and outlet of the canister provide a unidirectional flow of gases over the absorbent. In the To and Fro system there are no valves and the gases go back and forth. This method of anesthesia is described in greater detail in the next chapter.

RESISTANCE IN INHALATIONAL DEVICES

THE NATURE OF RESISTANCE

A pressure difference develops between the inlet and outlet of a tube when a particular volume of fluid passes through it. This pressure difference, referred to as *resistance,* is necessary to force or draw a fluid through the tube. The magnitude of the pressure is an index of the resistance. When the flow is purely laminar the resistance is linear, that is, it is directly proportional to the flow rate; when the flow is turbulent the resistance is no longer linear but varies with the square of the flow rate. If plotted graphically the curve would be parabolic instead of linear.

RESISTANCE IN INHALERS

Breathing in and out of a tube or other enclosures, such as inhalers used for anesthesia, requires more effort than breathing the same volume of gas directly from the atmosphere. This effort is in proportion to the resistance. The flow in an inhaler is seldom purely laminar though ideally it should be so. Most often it is both, laminar and turbulent with the laminar predominating. Resistance can be made minimal but it cannot be eliminated entirely from an inhaler. All inhalational appliances no matter how small have some degree of resistance. The resistance offered by an open cone is almost imperceptible; nonetheless some resistance is present.

FACTORS WHICH INCREASE RESISTANCE

Anything which impedes the flow of a fluid in a conduit and tends to convert the flow from a laminar to turbulent one increases resistance. Angulation of connectors, the presence of valves, roughening of surfaces of the tubes and variations in cross-sectional diameter of a tube introduce varying degrees of resistance. All openings, fittings, valve orifices, breathing tubes, connectors for
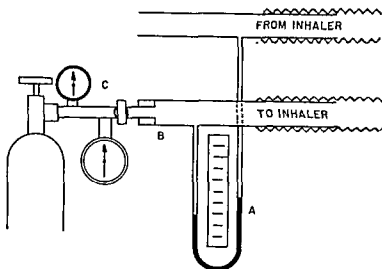
FIG. 9.3. Resistance is measured by intercoupling a manometer (A) between the inlet (B) and outlet (C) of an inhaler and measuring the pressure difference which develops when a gas is supplied at the inlet at a known flow rate. The outlet pressure is close to atmospheric. The inlet pressure is greater than that in the outlet and varies with the flow rate and degree of impedance offered by tubes, valves, soda lime, angulations and so on. The flow meter must deliver flow rates which can be varied from 5 to 100 liters per minute.

bags and masks on apparatus for inhalational purposes should be of a diameter equal to or should exceed the diameter of the human male trachea. Resistance is minimal when apertures and diameters of tubings are no less than 2.5 cm. Fittings for intratracheal catheters, likewise, should be of the same or should exceed the internal diameter of the intratracheal catheters.

MEASUREMENT OF RESISTANCE

CONTINUOUS FLOW METHOD

Resistance may be measured by using one of two techniques. Both have certain drawbacks which will be discussed. The commonest way of measuring resistance is to interpose a manometer between lead off tubes placed at the inlet and outlet of an inhaler (Fig. 9.3). The difference in pressure which develops when a gas, at a particular flow rate, is forced through is an index of resistance. Since at some point during the inspiratory and expiratory cycle the instantaneous flow of the gases of a patient breathing

forcefully may be as much as 80 or 90 liters per minute, studies must be done using such flow rates. Thus, the study is initiated using a flow of 5.0 liters per minute and is increased progressively in increments of ten liters. A sloping type of curve is usually obtained (Fig. 10.3).

The pressures developed in studies on resistance are, comparatively speaking, of small magnitude. For this reason a water manometer is used and resistance is expressed in terms of millimeters of water. Mercury manometers would be less sensitive and measurements would be more difficult to record. Data obtained using such a continuous unidirectional flow may be grossly misleading, however. The resistance which develops when the respiratory stream stops and is reversed is not taken into consideration by this technique of measurement. It is possible for the flow to be laminar in a direct, unaltering flow while it could be turbulent in the To and Fro. Therefore, a very important aspect of resistance remains undetermined if one places sole reliance on data obtained by this method.

Fig. 10.3. Type of curve obtained by using apparatus described in 9.3 for measuring resistance. Under ideal conditions the increase is linear when the flow is laminar. When flow becomes turbulent it increases as the square of the flow rate.
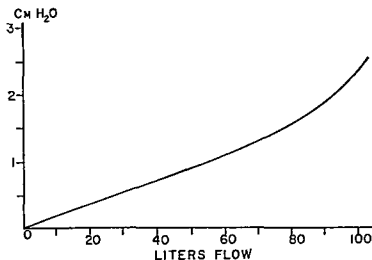
Likewise, the resistance which is introduced by opening and closure of the valves in inhalers so equipped is not measured. Ordinarily, more than half the resistance is introduced by the valves in an inhaler. Therefore, this important source of resistance is not adequately considered with this technique of study.

MANOMETER IN MASK TECHNIQUE

The writer prefers to measure resistance by placing the manometer at a lead off tube in the mask. As the patient inspires a negative pressure develops in the mask in proportion to the impedance offered. On expiration a positive pressure develops. Apparatus may be tested in the laboratory by using a mechanical respirator which simulates human respiration (Fig. 11.3). Such a device eliminates all variable factors by employing fixed tidal volumes, respiratory rates, times for the inspiratory and expiratory phases of respiration and other factors. A more realistic picture of the resistance due to the effects of inertia, turbulence from the starting and reversing of the stream of gases and sealing and unsealing of the valves is obtained. The discrepancies in the data obtained between these two techniques is remarkable. The latter method may show considerable resistance to be present in cases where the former indicates little or no resistance.
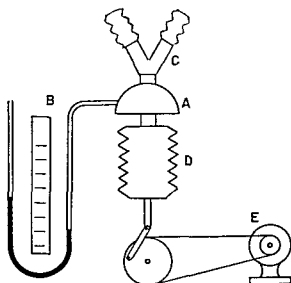
Fig. 11.3. Apparatus for manometer in mask technique of measuring resistance. The bellows (D) is calibrated to deliver the desired volume of gases. Motor (E) drives bellows and permits control of rate of respiration, duration of inspiration and expiration. Fluctuations in pressure are measured by placing manometer (B) in mask (A). The greater the resistance the greater the negative pressure which develops in the mask on inspiration and the greater the positive pressure on expiration.

The chief objection to this technique is the difficulty in eliminating errors due to inertia of the fluid in the manometer and accurate sighting of the meniscus. This can be reduced by using pressure transducers and optical and electrical methods of recording.

OTHER METHODS

Eastwood and his associates have suggested the use of the pneumotachograph for measuring resistance. Little data is available using this device because the pneumotachograph is unavailable in most laboratories.

"NORMAL" RESISTANCE

Resistance is an individual characteristic of an inhaler. Published data for a particular type of inhaler mean little since the performance of a piece of equipment is subject to many variations. There may be considerable differences between the resistance of two pieces of the same model of a given inhaler of a particular manufacturer. One set of values may be obtained when the apparatus is new; another when it has been in use some time. The type of valve used in its construction, its age, whether it is moist or dry and its position are among the many numerous factors responsible for wide fluctuations in data obtained.

The writer has compared the To and Fro type filter with the circle using the technique of measuring pressures at the mask. The conditions of testing were as follows: A tidal exchange of 500 ml. 20 times per minute with inspiration equalling expiration in a mask with 2.5 cm. right angle fitting, an 8×13 cm. canister filled with 6–8 mesh soda lime and a 5 liter breathing bag, caused a resist-

ance which created negative and positive pressure of 2.5 mm. H_2O to develop. In a circle filter under the same conditions the following values were obtained as each piece was added to the mechanical ventilator used for testing:

Mask and Y connector with 2.5 cm. aperture	-0.5 mm. H_2O
One—75×2.5 cm. corrugated rubber tube	-1.0 mm. H_2O
One—Saad type valve	-3 mm. H_2O
An 8×13 cm. cannister filled with 6–8 mesh soda lime	-4.0 mm. H_2O
The breathing bag	-4.5 mm. H_2O
The second flutter valve (Saad type)	-6.5 mm. H_2O
The second corrugated 75 $\times 2.5$ cm. tube	-7.0 mm. H_2O

The total resistance was 7 mm. H_2O. Generally a resistance total exceeding 10 mm H_2O is excessive for an adult.

FACTORS INFLUENCING RESISTANCE

EFFECT OF SODA LIME

Soda lime granules contribute only a small fraction to the total resistance. Resistance from this source may become excessive if granules of a fine mesh are used since they favor an increase in turbulence. The smaller granules absorb more efficiently but introduce greater resistance. A blend of 4–8 mesh granules has been shown, by experience, to be the most satisfactory for inhalational anesthesia.

LENGTH OF TUBE

Lengthening the tubing from 30″ to 36″ changed the resistance comparatively little. Doubling the length added a resistance equivalent to 2 mm. H_2O.
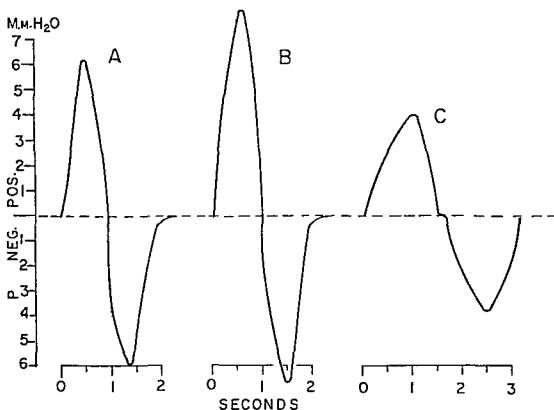
Fig. 12.3 (A) Resistance at 500 cc. tidal volume and respiratory rate 30 times per minute. (B) Resistance at 750 cc. tidal volume and respiratory rate 30. (C) Resistance with respiratory rate 20 times per minute and tidal volume 500 cc.

TIDAL VOLUME

Resistance increases with tidal volume (Fig. 12.3). The greater the tidal volume the greater the resistance, since the volume flow is increased. If the respiratory rate is doubled but the tidal volume halved from 500 ml. the resistance is less than if the tidal volume is increased to 1000 ml. but the rate halved. The minute volume exchange is the same in both cases but the flow rate at the height of the acceleration of the gases is much higher with the larger tidal volume. Not only must twice as much gas flow through during the same space in the same time interval, but the flow is in some areas converted from laminar to turbulent. An increase in respiratory rate also increases the linear velocity and, therefore, resistance. The

deeper and more rapidly a subject breathes into a closed system the greater the resistance which develops (Fig. 12.3).

CANISTER SHAPE

The shape of the canister, size of outlets and position has considerable influence on resistance. The walls of the canister should be straight and smooth. Oblong, spherical, cylindrical and oval shaped canisters are the most satisfactory from the standpoint of resistance. Cylindrical canisters narrower than 7 cm. diameter filled with absorbent add resistance as the diameter decreases. This is particularly true when the canister is made longer to accommodate the tidal volume.

By far the greatest amount of resist-
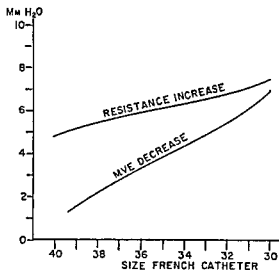
Fig 13 3. Undersized endotracheal catheter introduces additional resistance to respiration. Increased effort must be made to maintain the blood gas tensions and the minute volume exchange at normal levels.

ance is introduced by valves. This is discussed later in this chapter.

Size of Endotracheal Tubes

Endotracheal tubes may introduce considerable resistance if not of the proper size and type. As the diameter of a tube is decreased, a critical point is reached at which a laminar flow is replaced by a turbulent flow throughout the *entire length of a tube. The flow of air* at a flow rate of 14 liters per minute, for example, would be laminar if passed through a tube one centimeter in diameter; while it would be turbulent if passed through a tube half a centimeter in diameter. For the flow to remain laminar at this diameter the flow rate would have to be reduced one-half. In addition to the diameter of the tube, critical flow rate also depends upon the ratio of viscosity of the gas to density. In the case of air, the ratio is 0.018/.0012 or 15. A value, known as the *Reynolds number* or Reynolds criterion, is used by engi-

neers as a guide for computations of flow rates of fluids through tubes of various diameters. The critical velocity range above which a fluid flow will be turbulent and below which it will be laminar depends upon the velocity of flow, the size and shape of the conduit and the viscosity. Reynolds established the fact that at a given temperature for geometrically similar flows

$$\frac{velocity \times length}{kinematic\ viscosity}$$

is the same for all fluids at the critical velocity. The same scale must be employed for indicating *velocity* and *length* of conduit for each fluid studied.

Resistance in Endotracheal Tubes

An undersized endotracheal catheter may permit the passage of a minute volume exchange which is adequate as far as blood gas tensions are concerned. The respiratory effort, however, to maintain this exchange may be increased appreciably. An increased intrapulmonic negative pressure is necessary to offset an increase in resistance (Fig. 13.3). Therefore, such added resistance is harmful. Slight degrees of resistance may be endurable for short periods of time in patients who are "average good risks." Acutely ill subjects may ventilate inadequately if they cannot make the extra effort. Negative pressures in the order of 40 mm. Hg in the pleural space may develop to compensate for the resistance in order to maintain normal blood gas content. Pulmonary edema may result from excessive resistance to inspiration.

Additive Effects

If two tubes each having a resistance of 1 mm. H_2O are placed in series the
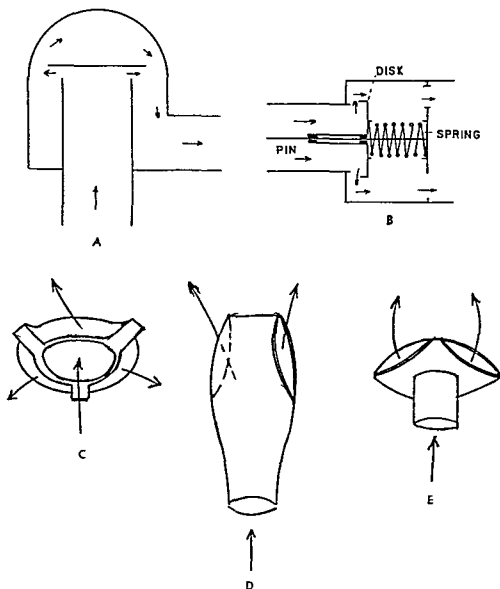
Fig. 14.3. Two basic types of respiratory valves. (A) Disk (gravity) lift, (B) Disk (spring fixed), (C) J valve, (D) Flutter (Saad) and (E) Flutter (mushroom).

resistance does not necessarily add up to 2 mm. H₂O. Usually it is more. In other words, the two pieces together may cause more turbulence than either alone. The same principle applies to valves, fittings and adaptors.

RESPIRATORY VALVES

BASIC TYPES

Inspired gases may be separated from expired gases which pass into a common enclosure, such as a mask, by valves which create a unidirectional flow. There are almost as many designs of valves as there are inhalational therapy devices which employ them. These have been referred to as knife edge, spring loaded, cage disk, rubber sleeve, rubber flap types and so on. However, each of these specific valves is one or the other of two basic types—the *"disk"* and the *"flutter"* (flap) valve. A cross between the two types embodying some of the features of
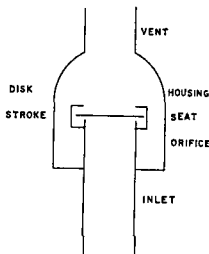
FIG. 15.3 Essential parts of a valve.

both is also used. The disk valves are usually seated by gravity. In some valves the disks are fixed by a central pin or by a spring or both (Fig. 14.3). In others the disk is fixed by slips of rubber which supply the recoil (Fig. 14.3). The disks are made of light metal, hard rubber, plastic or other rigid durable substance. The flutter valve is composed of two closely approximated rectangular sheets or flaps of an elastic substance, usually latex or moulded rubber. These flaps are adherent at a number of points and are, thus, held together in such a manner that an ovoid opening is created when they are spread apart. One end is shaped into a tube which slips over the inlet tube for delivery of the gas (Fig. 14.3). The ambient gases force the flaps apart and escape in a sidewise direction through the ovoid or circular opening which they create as they pass out from the inlet tube. Gases flowing in the reverse direction compress the flaps together thereby effecting a seal. Closure is aided in part by the elastic recoil of the rubber. The size of the opening created when the flaps spread apart may

also be influenced by the elasticity of the rubber. Flutter valves may be placed in any position. A cross between the disk and the flutter types utilizes a single flap fixed at several points on a rigid tube (J. valve). The seating may be positional (horizontal) or non-positional, vertical or inverted in this type. The seating disk in other valves may be attached at one point and operate in a hinge-like manner.

The essential parts of a valve assembly are (Fig. 15.3) (1) the *housing* which encloses the (2) *valve* and (3) its *seat* to which are fixed the (4) *inlet* and (5) *outlet* flow connections. (6) The *vent* which collects the gases after escape through the valve is the part of the housing surrounding the outlet. The distance the disk is lifted from its seat or the flaps are separated is known as the *stroke*. The diameter of the inlet tube which forms the seat is referred to as the *orifice*. Guide pins, cages and stops of various sorts are used to limit the stroke and maintain the proper position over the seat in the disk type valve.

Individual Type Valves

Gravity Lift Valves

The horizontal *disk type*, known as "gravity lift" valve, appears to be the most popular and is found in practically all types of anesthetic apparatus, as in that of McKesson, Heidbrink, Foregger and Connel. The seating device consists of a disk of aluminum, plastic, hard rubber or other light substance which fits snugly over a knife edge. The disk rests horizontally (Fig. 14.3). Cages, wire leads or stops guide the motion of the disk up and down and hold it in position and limit its stroke. Difficulties may arise with this type valve in the sealing

and closure. The Bailey valve was designed to improve the seal and prevent leakage.

The Bailey Valve

The Bailey valve is in essence a gravity lift disk valve. It consists of a cuplike affair inverted over the inlet tube. The edges of the cup rest on a pool of mercury which surrounds the inlet tube in a moat-like fashion (Fig. 16.3). The incoming gas lifts the cup from the surface of the mercury as it passes through the valve. On closure the cup falls back into the mercury and its edges dip below the surface. A tight seal is thereby assured. The Bailey valve has a number of disadvantages, as far as its use in anesthesiology is concerned. It must be fixed in order to avoid spillage of the mercury. When the patient hyperventilates mercury tends to splash into the inlets.

The Saad Valve

The most widely used of the flutter valves is the Saad valve consisting of two flat pieces of rubber cemented at several points so that openings are created for the ambient gases when the sheets are forced apart (Fig. 14.3).

Mushroom Valve

The Henderson and Haggard valve consists of a circular rubber disk attached to a collar-like flap at several points. This is attached to a rigid rubber collar-like inlet tube which is attached, in turn, to the inlet tube (Fig. 14.3). This is sometimes referred to as the "mushroom valve" due to its mushroom like appearance. Both the Saad and mushroom valves operate in any position, including the inverted, since they do not require gravity for closure.
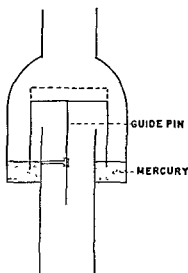
Fig. 16.3. *Bailey valve (see text). The mercury seal prevents leakage.*

J. Valve

Another type valve employs a single rubber flap over an inlet tube fastened by slips of rubber which act as grips. This, as has been mentioned, is a cross between the flutter and disk valve. It too is non-positional and operates effectively in the horizontal, vertical or inverted position.

POSITIVE PRESSURE EXPIRATORY VALVES

Resistances are sometimes placed on the expiratory valve of semi-closed inhalers to create expiratory positive pressure. This is accomplished by (1) placing an adjustable spring in the housing over the disk of the valve (spring loading), (2) by attaching calibrated weights to the disk which can be varied in size, and (3) by providing a constricting orifice for exhalation whose size may be varied. This orifice is calibrated in centimeters of water pressure. The O.E.M. mask used for oxygen therapy and Neff valves on the Foregger circle filter embody this type valve.

PERFORMANCE AND DEFICIENCIES OF VALVES

Valves are indispensable in a circuit system and in "non-rebreathing" devices. There are a number of valid objections to valves. Some of the more pertinent objections are: (1) They fail to seal properly or at the proper time, thereby causing some leakage or regurgitation in the reverse direction. Such a leak is tantamount to increasing the dead space. The greater this "backflow" the greater the amount of rebreathing. (2) Valves create resistance (a) by obstructing the gas flow by whatever inertia they possess, (b) by failure to open properly (sticking) due to surface tension effects, (c) by having an orifice of inadequate diameter which restricts the flow and (d) by diverting the flow so that it is no longer laminar, thereby creating turbulence. Most of the resistance in anesthesia apparatus is introduced by the valves. The To and Fro closed inhaler is devoid of this objection.

OPENING PRESSURES AND RESISTANCE

Ideally speaking, all respiratory valves should require no opening pressures. Inertia is always present, however, but it can be reduced to a minimum by having valves as light as possible. They should be seated in such a manner that there is minimal or no leakage during the phase of respiration requiring closure. However, if they are too light there may be a lag in sealing, particularly in the gravity lift type. Experience has shown that the cross sectional area of the potential aperture in a valve should be 6 sq. cms. or more to eliminate the resistance.

Leakage in Valves

Leakage or regurgitation may be of two types—static and dynamic. *Static* leakage occurs when a negative pressure is applied to the inlet of the valve and gas can be drawn back while the valve is at rest and supposedly sealed. It is due to improper sealing. *Dynamic* leakage occurs when the valves fail to close promptly and properly at the end of expiration. Wetting usually improves the seating of disk valves and closure of the flutter valves but tends to increase the opening pressures, since the surface tension of water on metal or rubber must be overcome. Opening pressures of valves have been variously quoted from 0.1 to 5 or 6 mm. water. The greater the pressure necessary to open the valve, the greater the effort which the patient must expend and the more the resistance. Data on resistance to air flows, leakage, opening pressures for a particular type valve are not absolute or constant since they vary with operating conditions and these are notoriously variable during clinical use. Two valves of identical design and manufacture may vary widely in resistances, opening and closing pressures and amount of leakage. One set of values may be obtained for a particular valve under one set of experimental conditions and another when conditions have been slightly altered. The performance of valves changes with time and usage. Rubber valves particularly undergo deterioration, become sticky or rigid and thereby change their efficiency. Metal valve seats in disk valves are subject to wear and therefore have disadvantages also.

EFFECT OF POSITION OF VALVES

Valves may be placed proximally at the mask or distally at the canister in closed systems. In semi-closed inhalers they are placed at the mask. Placement at the mask obviates the tendency of the

breathing tubes to recoil and collapse during inspiration and to expand during expiration. The gravity lift type is impractical for use at the mask. When disks are employed at the mask a central pin is used for guidance. Semi-closed inhalers of the type having the inlet port in the dependent (in the breathing bag) position (O.E.M. mask, Cyprane inhaler, etc.) (Fig. 1.3) may employ a disk gravity lift type at this opening. The outlet valve must be of the flap type unless a guide pin is used. In the circle system a Y piece is necessary to divide the stream of gases. The valves may be incorporated into the Y piece. Valves placed at this site must be of the flap type since they *must function in any position.* If the disk type is used it must be held in position on the seat by a pin. They must also have springs to assist in closure. The J valve may also be used at the mask since it too is nonpositional. The stability of the valve housing is sacrificed and the valves are cumbersome when placed at the mask. The valve housing should always be transparent so that operation of the valves is always under surveillance.

THE ENDOTRACHEAL CUFF

Pressures in the Cuff

The endotracheal cuff is a device designed to effect a seal between the exterior of the tracheal catheter and the inner tracheal wall. A variety of designs are available but they may all be resolved into two basic types, (1) *self-inflating* and (2) *inflatable.* The self-inflating cuff traps air in a thin latex sheath which has been cemented to the wall of the tube and causes a balloonlike effect between the trachea and the catheter. The inflatable cuff is the more practical

of the two types and more widely used. It consists of a double layer of latex with edges sealed to make a balloon. This balloon is slipped over the outer surface of the distal end of the catheter. A long thin catheter communicates with the balloon through which measured volumes of air are introduced to inflate the cuff. Pressures necessary to inflate the conventional endotracheal cuff to effect a seal vary widely from cuff to cuff. Much depends upon the quality, thickness and age of the rubber. The volume of air needed depends upon the ratio of tracheal diameter and catheter size. The pressures necessary to effect a seal between the trachea and catheter wall to *maintain* pressures of 15 and 20 mm. Hg in a circle system range between 90 and 200 mm. Hg. The wide latitude of pressures necessary is due to the differences in the elasticity of the rubber, the thickness of the rubber, the differences in the size of the cuffs, the differences in volumes of air necessary to inflate the cuff, and differences in the distance between the outer cuff wall and the trachea. The lateral pressure exerted by the cuff itself on the tracheal wall is a more constant value and bears no direct relationship to the intracuff pressure. This pressure ranges between 10 and 15 mm. Hg when inflated to the point which causes a seal that maintains pressures ranging between 15 and 20 mm. Hg in the inhaler and trachea (Fig. 17.3). After this minimal pressure necessary to effect the seal has been attained the lateral pressure on the interior of the trachea rises in proportion to the intracuff pressure if additional air is introduced into the cuff. This pressure may become so great that it tends to stretch the trachea and to compress the capillaries and arterioles in the mucosa. Ischemia and possibly
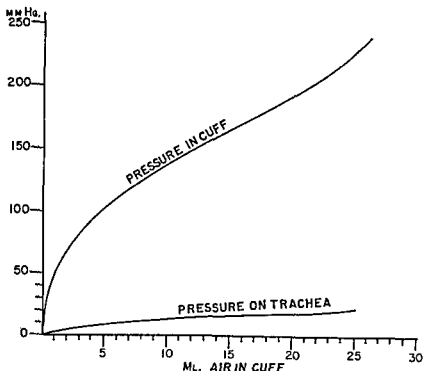
FIG 17.3 The pressure within a conventional latex endotracheal cuff contrasted with that exerted upon the trachea by the cuff.

necrosis of the tracheal mucosa may result.

Attention has been called to possible trauma which might result in contusions and lacerations to the trachea, bronchi or alveoli by rupture of a cuff. However, the ill-effects of these complications have been grossly exaggerated. Ordinarily less than 10 ml. of air are necessary to inflate most cuffs. Forty ml. or more air are necessary to rupture most latex cuffs. Such volumes ordinarily generate pressures not exceeding 250 mm. Hg. Intracuff pressures exceeding 1000 mm. Hg, generated by volumes as great as 40 cc., even when the cuffs were ruptured caused no discernable trauma to the trachea, bronchi or lungs of dogs.

SEALING EFFICIENCY OF THE CUFF

The cuff is 100% effective in preventing the aspiration of gastric contents and other secretions from the pharynx into

the trachea. This has been verified by the preoperative administration of dyes into the stomach and attempting to identify the dye in the pharynx and the trachea.

OBSTRUCTIVE EFFECTS OF CUFFS

The routine use of an endotracheal catheter of a single size for all patients has been suggested by Beecher. He suggests a 32 F catheter. Even without a cuff, such a catheter offers enough resistance to the respired gases to cause a measurable decrease in the minute volume exchange and an increase in ventilatory effort. Resistance increases progressively as the diameter of the catheter is decreased in an airway of constant internal diameter. This increase in resistance occurs even though the space between the catheter and the tracheal wall becomes greater and the gases are free to pass around the catheter. This is un-

derstandable, since, as the internal diameter of a catheter decreases the critical point is approached at which the flow ceases to be laminar and becomes turbulent. Equipping a catheter with an inflated cuff causes a still greater increase in resistance because the portion of gases passing around the catheter, in the case of the uncuffed catheter, must all pass through the catheter.

DIFFUSION OF GASES THROUGH NON-LIVING MEMBRANES

The thorough mixing of gases and vapors to form a homogeneous mixture, which is so essential in anesthesia, is accomplished by the physical phenomenon of diffusion. The heaviest vapor and the lightest gas become intimately mixed within a short time and behave as described by the laws of Fick, Dalton and Graham.

Gases diffuse not only into other gases, but also through liquids, and, in some instances, even through solids. The diffusion through liquids is an important factor in considering diffusion in the tissues. The membranes of the lungs, blood vessels and other organs are chiefly water. The diffusion of gases through living *membranes is described in* Chapter 4.

The diffusion of gases through non-living substances, such as solids and liquids, depends upon the porosity of the substance, size and weight of the molecules, and the solubility of the gas in the substance. An extremely light but rapidly diffusing gas, such as helium, may *diffuse through glass, which is not* porous in the ordinary sense. Low density gases may leak at slip joints and sleeve connections with ease while the same structures may be impervious to heavier gases.

PERMEABILITY OF RUBBER

The solid of interest in anesthesia through which diffusion occurs is rubber. Rubber is permeable to most gases used in anesthesia. Inasmuch as anesthesiologists rely upon rubber for reservoirs and conduits for vapors and gases, this aspect of diffusion through solids is important. Permeability of a rubber membrane to a gas varies not only with the type of gas but also with the thickness, composition and age of the rubber. The addition of carbon and other materials to render the rubber conductive also alters the permeability. Aging of a film of rubber is usually accompanied by a decrease of permeability to gases. The *permeability of a particular gas is in* direct proportion to the partial pressure in its relation to the constant total pressure. The diffusion of hydrogen, the lightest gas known, through a rubber bag varies inversely as the thickness of the rubber. An increase in temperature causes an increase in the rate of diffusion. Hydrogen diffuses through the same rubber bag twenty-two times faster at 100°C. than at 0°C. The permeability of rubber to certain vapors may be much greater than to the inert inorganic gases since the majority are organic compounds and may combine with or dissolve in the rubber. The hydrocarbons and ethers, for example, dissolve in rubber. Water vapor diffuses through rubber about five times faster than hydrogen. Wineland and Waters studied the diffusibility of anesthetic gases through rubber by noting the comparative loss *of weight from a 10 liter rubber bag* filled with the gases over a forty-eight hour period. The loss of oxygen was found to be 0.32 grams, ethylene 1.00 grams, carbon dioxide 4.6 grams and nitrous oxide 7.00 grams.

The Behavior of Gases and Vapors in Body Fluids and Tissues

SOLUBILITY AND DIFFUSION

CONCENTRATIONS OF GASES IN TISSUES

THE BEHAVIOR of gases in tissues and body fluids is an important consideration in anesthesia and inhalation therapy. A constant interchange of gases occurs between the cells and the external environment through the medium of the extracellular fluid and blood. The molecules of each component gas of a mixture of gases become distributed evenly in a homogeneous medium in accordance with the laws of diffusion. Each gas present in such a medium exerts its own partial pressure. The sum total of all the pressures of each component gas in the pulmonary alveoli, blood, and cells equals atmospheric pressure (760 mm. Hg).

METHODS OF EXPRESSING CONCENTRATIONS OF GASES

The concentration of a gas in a mixture of gases or in a liquid may be expressed in one of three ways. One may refer to the *weight of the gas* in grams or other units of weight per unit volume. This is an absolute and constant value, since it is an index of the number of molecules present. One may express the concentration by indicating the *partial pressure* the gas exerts in millimeters of

mercury. This, again, is a constant value, since it is also a reflection of the total number of molecules present. One may use a third method of designation and refer to *the percent composition* of the gas. The term *volumes percent* refers to the units of volume of a gas per 100 units of volume of a substance. This is not an absolute value since it is not a reflection of the number of molecules present. Oxygen is present in air in a concentration of 21 ml. per 100 ml., or 21 volumes percent. The pressure exerted by the oxygen is 21% of atmospheric pressure (760 mm. Hg) or 150 mm. Hg. The concentration of a gas in terms of volumes percent does not necessarily indicate the amount (weight) of a gas present because this varies with changes in atmospheric pressure. Thus, at sea level the tension of each component gas in the atmosphere is much greater than at a high altitude but the percentage composition in volumes percent of each gas remains unchanged at each elevation. An 80% nitrous oxide and 20% oxygen mixture may be effective for anesthesia at sea level but ineffective at higher altitudes. The number of milligrams of nitrous oxide which dissolves in plasma is much less at the reduced barometric pressure even though the percent com-
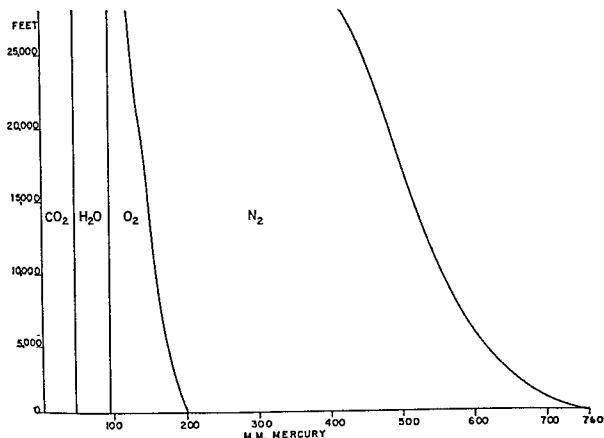
FIG. 1.4. Variations in alveolar tensions when a mixture composed of 21% oxygen (by volume) and an inert gas is inhaled at different altitudes. The inhaled percent composition does not vary at any altitude. The amount of each gas which dissolves in blood is proportionate to the partial pressure and, therefore, varies with changes in altitude. Alveolar carbon dioxide and water vapor tensions remain constant.

position is the same as at sea level (Fig. 1.4).

DETERMINATION OF CONCENTRATION

Concentrations of gases in fluids and tissues may be determined by a variety of techniques. Usually they are analyzed directly (see Gas Analysis) by determining the amount of physically dissolved gases. However, they may also be determined by equilibrium techniques. In equilibrium techniques a small bubble of a gas is mixed with the blood or fluid whose gas tension is to be determined in a chamber called a *tonometer*. The volume in the bubble is minute compared to the volume of fluid used. The

gas to be analyzed passes into the bubble. After time for equilibration has elapsed the gas tension in the bubble is determined by direct analysis.

PRESSURE GRADIENT

A gas diffuses from the blood to tissues, and vice versa, only if a pressure gradient exists for that gas between these points. The greater the difference, that is, the steeper the gradient, the more easily the interchange occurs. Blood merely acts as a medium of transport for gases and vapors between the lungs and tissues. The oxygen in the atmosphere exerts a pressure of 152 mm. Hg. In the alveoli the pressure is 105
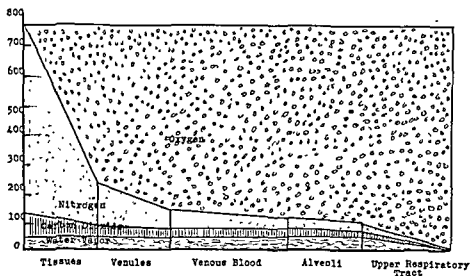
Fic. 2.4. The inhalation of one hundred percent oxygen by the semi-closed system causes a displacement of nitrogen from the alveoli and blood. A pressure gradient is thus established between tissues and blood. This favors the elimination of intracellular nitrogen. Note that the partial pressure of nitrogen in tissues is high even though the quantity of nitrogen in tissues is small. Nitrogen does not combine with any substance in the body and is relatively insoluble.

mm. Hg; in the blood it is 90 mm. Hg; in the tissues it is zero. The diffusion is from the outside air, to the alveoli, to the arterial blood and thence to the tissues. Interchange of gases between the atmosphere and the pulmonary alveoli is augmented by variations in pressure within the thoracic cage caused by the respiratory excursions. This accentuates the diffusion by attempting to equalize the tension of the gases in the lungs and outside air, thus establishing a steeper gradient between the alveolar air and blood. Thus, a higher gradient is established between the alveolar gases and the blood by the respiratory movements than could be attained by simple diffusion. In spite of the respiratory exchange, the composition of the alveolar gases remains remarkably constant. The inward movement of gases from the air to the alveoli, then, is aided by mechanical means. On the other hand, the passage of gas to tis-

sues from the alveoli depends solely upon the diffusibility through the cells.

The same principles apply to the elimination of gases. The gases in the tissues are at a higher gradient than in the blood and in the blood they are at a higher gradient than in the alveoli. The mechanical mixing caused by the respiratory movements helps establish a steep gradient from the blood to the outside air.

The partial pressure of carbon dioxide in the atmosphere is almost zero; that in the alveoli is 40 mm. Hg at ordinary atmospheric pressure; and that of the venous blood is 46 mm. Hg. The gradient, therefore, is from the blood to the alveoli to the outside air. The partial pressure of carbon dioxide in the tissues varies. It may be as high as 60 or 70 mm. Hg. Diffusion of carbon dioxide, therefore, is from the tissues to blood (Fig. 2.4). If the partial pressure of carbon

dioxide in inhaled air is increased, the pressure gradient for the gas from blood to alveoli is decreased and the alveolar tension rises above normal. If the per-cent inhaled is sufficient to raise the alveolar concentration 0.1% by volume, enough carbon dioxide accumulates in the tissues to stimulate respiration.

The same principles apply to the absorption and elimination of other gases and vapors which pass into or from the tissues. Nitrogen, helium and anesthetic *gases and vapors diffuse in and out of* the body in the same manner as do oxygen and carbon dioxide.

DIFFUSION RESPIRATION

The transport of gases to and from the tissues is augmented by the respiratory *movements. In the absence of respira-*tory movements (induced by curariza-tion) the interchange still occurs, but at a more gradual rate, since the gradient from the outside air to the alveoli is a declining slope instead of a steep one. The inward diffusion of oxygen may be accelerated by creating a steeper gra-dient by flooding the mouth and nares with 100% oxygen. It is the gradient, and not the total amount of available oxy-gen, which determines the amount of diffusion. In the alveoli the absorption of oxygen is rapid due to its solubility and ease of combination with hemo-globin. This causes the tension in the alveoli to fall. This pressure differential augments the diffusion into the lungs from the trachea and mouth. Draper and Whitehead have studied this phenom-enon in dogs and have termed it *diffu-sion respiration*. Oxygenation was ade-quate but the outward diffusion of car-bon dioxide remained unchanged and a retention occurred. These writers claimed that the hemoglobin effect cre-ates a negative pressure and have re-ferred to it as the "hemoglobin pump."

DIFFUSION COEFFICIENTS

The rate of diffusion of a gas into a liquid is directly proportional to the ab-sorption coefficient (solubility of the gas) in that liquid and inversely proportional to the molecular weight of the gas. While it is true that cells are largely water, and that solubility plays the dominant role, *solid constituents are present which alter* this concept. The diffusion of gases through a cell membrane and protoplasm is difficult to estimate because the com-position and physical nature of proto-plasm vary from species to species and from tissue to tissue, and even for a given particular tissue under different conditions. Krogh has defined the *diffu-sion coefficient* of oxygen through tissues as the number of cubic centimeters of the gas which diffuse 0.001 mm. distance over a square centimeter of surface per minute at one atmosphere pressure. The diffusion coefficient of a particular gas through the pulmonary epithelium may be defined as the number of cubic centi-meters of the gas absorbed per minute per millimeter of pressure difference be-tween blood and alveolar air. The co-efficient varies in different individuals due to variations in the capacity of the lungs, patency of the capillaries, area of alveolar membrane and other physiologi-cal factors. The coefficient for oxygen through pulmonary epithelium at rest is between 25 and 45; for carbon dioxide it is approximately 500. It must be noted that carbon dioxide has a greater water *solubility than oxygen. The diffusion co-*efficients for volatile anesthetics have not been studied. Little reliable data is

available. All the common anesthetic gases and vapors, however, pass with ease through living membranes into the blood.

TRANSPORT OF INERT GASES IN BLOOD AND TISSUES

Gases are carried in blood either by simple solution or they are reversibly combined with some constituent in the blood. Chemical combination permits a greater amount of a gas to be transported by the blood than would be allowed by mere simple solution. Approximately 19 volumes percent of oxygen is carried by the blood normally. Only 2.4 volumes percent of this are carried by simple solution; the remainder is carried in association with hemoglobin. Nitrogen is chemically inert and combines with no particular substance normally present in the blood and tissues. This gas is, therefore, carried entirely by simple solution.

Anesthetic gases and vapors behave like nitrogen in this respect. They are chemically inert and are carried by simple solution in the plasma to the tissues. Volatile anesthetic drugs are distributed in the cells and plasma according to their solubility in the various substances composing the cell. For example, the red cells carry approximately 2½ times as much cyclopropane or ethylene as does the plasma. Ether, on the other hand, since it possesses a relatively higher degree of water solubility, is distributed almost equally between the plasma and cells. Chloroform is found in greater concentration in the cells than in plasma. This greater predominance of some anesthetic drugs in the red blood cells is most likely due to their greater solubility in lipoids inasmuch as the erythrocytes are rich in lipoids. The solubility of a lipophilic anesthetic like cyclopropane varies with the hemoglobin content of the blood.

ABSORPTION OF VOLATILE INERT ANESTHETICS AND GASES

Inhalational anesthetics are chemically inert in the body. They undergo no significant alteration in structure and are released unchanged, almost quantitatively, through the lungs. The amount excreted by the kidney, through the skin, into the bowel and by salivary and sweat glands is relatively insignificant. Their absorption and elimination from the lung are basically the same as and follow the same physical laws applicable to the inert non-anesthetic drugs.

FACTORS INFLUENCING ABSORPTION

The depth of anesthesia using volatile, inert anesthetics is directly dependent upon the tension of the drug in the brain. The tension in the brain, when anesthesia is fully established, is at equilibrium with that of the arterial blood The arterial blood tension, in turn, is at or near a point of equilibrium with the gas tension in the alveoli. Thus, the tension of the drug in the brain is directly dependent upon the alveolar tension. The tension in the alveoli in turn depends upon the pulmonary ventilation.

The amount of a gas or vapor which diffuses through the alveoli into the blood depends upon the percent of the minute volume exchange which reaches the alveolar surface and the concentration of the drug in it when it reaches the alveolar membrane. The higher the concentration, the steeper the pressure

gradient. The volume of air in contact with the pulmonary epithelium is called the *functional residual air volume*. The inspired air (tidal air) mixes with the functional residual air. The tension in the alveoli depends on how much of the inspired volume mixes with the functional residual air volume. The smaller the functional residual air volume is in relationship to the inspired air volume the more readily and rapidly the mixing occurs. When the tidal volume is proportionately less than the functional residual volume, mixing is slower and the resulting alveolar pressure gradient is not as steep.

SIZE OF THE DIFFUSION SURFACE

The size and the state of the pulmonary diffusion surface is important because the amount of gas which passes into the blood depends upon how much of the gas comes into contact with, and how easily it passes through, the pulmonary epithelium. If maldistribution of the gases occurs in certain areas of the lung and some of the inhaled gases do not reach the functioning respiratory epithelium, even though the perfusion of blood through the area is adequate, the interchange of gases does not proceed as it should.

Ordinarily, diffusion of anesthetics through a normal pulmonary alveolar membrane takes place with ease. Differences in the numerical values in the diffusion coefficients of the various anesthetics across living membranes are of no apparent consequence, as far as diffusion is concerned, since it occurs easily and quickly with all anesthetics. Abnormalities of the membrane, such as edema, thickening or areas of fibrosis may interfere with diffusion and retard it or prevent it, however.
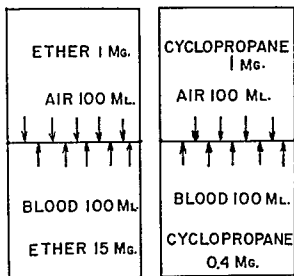
FIG 34 The air blood ratio (solubility coefficient) is the ratio of the distribution of a gas or vapor in identical volumes of a gaseous and liquid phase at equilibrium. For ether distributed between air and blood at 37° the ratio is 1·15.

DISTRIBUTION COEFFICIENT

After the gas has passed through the alveolar epithelium it passes through the endothelium into the capillaries. Once in the capillaries the drug dissolves in the blood. The amount which dissolves in the blood depends upon the distribution coefficient (Chap. 1). The *distribution coefficient* is the ratio of the concentration of the gas in the blood to the concentration of the gas or vapor in air when an equilibrium has been established between equal volumes of mixtures of air and volatile drugs and the blood (Fig. 3.4). Ether, one of the most water soluble of the inhalational anesthetic gases, has a solubility coefficient of 15. By this is meant that 15 parts of ether are present in blood to one in air when equal volumes of blood and air are equilibrated. This ratio differs for each anesthetic drug. For cyclopropane it is 0.4 to 1.0; for ethylene it is 0.12 to 1.0; for chloroform it is 10 to 1.0. Drugs
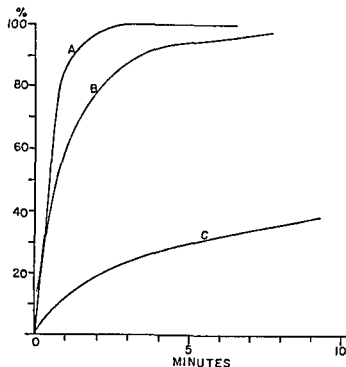
FIG. 4.4. (A) Rise in alveolar concentration of a gas insoluble in blood and water. The plateau does become a horizontal line. (B) Rise in the alveolar concentration of a gas having a low solubility coefficient. The plateau which results when the lung is filled with the gas continues to slope upward until blood and tissues are saturated (C) The alveolar concentration of an inhaled gas or vapor highly soluble in blood and tissues rises gradually.

having low solubility coefficients quickly saturate the blood, particularly if the partial pressure required for anesthesia is high. Ethylene requires a partial pressure of 650 mm. Hg for anesthesia and possesses a low solubility coefficient. Induction and recovery, as clinical experience shows, are rapid with this drug, requiring only 2–3 minutes. The total amount of a gas or vapor which passes from the alveoli into the blood is dependent upon the solubility of the gas in blood, the total amount of blood to which the gas or vapor is exposed and the rapidity of blood flow through the lungs. The more soluble a gas is in blood, the more easily it is carried away from the alveoli. Therefore, the alveolar tension of a relatively highly water soluble gas like ether increases slowly since it is so soluble and is carried away rapidly. Induction, therefore, is slow.

If a constant concentration of a poorly soluble gas mixture is inhaled through a non-rebreathing valve, assuming that

the blood absorbs none of the gas, there is a rapid increase in the concentration in the lungs as the other gases are displaced. A steeply rising curve terminating in a plateau results (Fig. 4.4) This plateau represents the point at which the concentration of the gas supplied to the inhaler and that in the lungs are equal. This condition, however, never is attained in clinical anesthesia because anesthetics all possess some degree of blood solubility and the pulmonary blood flow depletes the alveolar tension by absorbing and distributing the drug to the tissues. The steep rise in the curve ends in a gradual slope instead of a plateau (Fig. 4.4).

BLOOD FLOW THROUGH THE LUNGS

Thus, another factor enters into the picture—the factor of adequate pulmonary perfusion. Adequate perfusion depends upon the volume of blood passing through the lungs, the circulation time

and the patency of the capillaries. The pulmonary blood flow depends upon the output of the right side of the heart since all of this goes through the lungs. The pulmonary blood flow carries the gas from the lungs to the left side of the heart and thence to the tissues. The amount of a particular drug of a given solubility absorbed by a given volume of blood will depend upon the duration of exposure; in other words, the circulation time. This varies with the physiological state of the individual. Circulation time is of such rapidity, however, that fluctuations in rate ordinarily encountered are, even in disease, slight in comparison to the over-all rate. Changes in the calibre and patency of the vessels in an area of the lung, such as might be caused by sclerosis or fibrosis, may cause inadequate perfusion of that area. Gaseous exchange cannot occur in that area even though ventilation is adequate and pulmonary circulation time and cardiac output are normal.

ABSORPTION BY THE TISSUES

The amount of a gas or vapor which passes into a particular tissue depends upon the mass of tissue, the solubility of the gas in it and the blood flow through the tissue. Most volatile anesthetics are *lipophilic*, that is, they are highly fat soluble and poorly water soluble. Volatile anesthetic drugs are listed according to the magnitude of their oil-water distribution coefficients. The higher the coefficient the greater the potency, as a rule. The uptake of anesthetic by high lipoid content tissues, therefore, is greater than that of the low lipoid content tissues. The rapid uptake of a highly fat soluble anesthetic causes the concentration in the blood to remain at a low level. This in turn favors the mainte-

nance of a low alveolar tension. Should the anesthetic have a low tissue solubility, or should the total mass of tissue be low, the tissue will be saturated quickly. The arterial blood concentration then rises. The concentration in the venous blood rises and tends to approach that of the arterial. Since the venous blood is returning to the lung with an increasing amount of drug the alveolar tension begins to rise. In due time equilibrium is established between the alveoli, venous blood and arterial blood (Fig. 5.4). The solubility in the tissues, however, means little if perfusion is inadequate. Organs and tissues with a profuse blood supply are more easily saturated than those with a poor blood supply. Nervous tissues, particularly those composing the brain, have a profuse blood supply. Each 100 grams of brain has at least a 50 cc. blood flow per second. Equilibrium is established between the blood and brain before it is with other tissues. The muscles and viscera have an excellent blood supply also. Relatively speaking their lipoid contents are low. They, however, saturate quickly with lipophilic drugs. The adipose tissues, in spite of their great affinity for anesthetics, have relatively speaking, the poorest blood supply of the soft tissues and may, therefore, be the last tissues to become saturated and desaturated.

ABSORPTION BY THE BRAIN

Emphasis has been placed upon the fact that the concentration of drug in the brain determines the depth of anesthesia. The tension in the brain, as is the case with other tissues, depends upon the cerebral blood flow and the tension in the arterial blood. The cerebral blood flow depends upon the arterial blood pressure and upon the re-
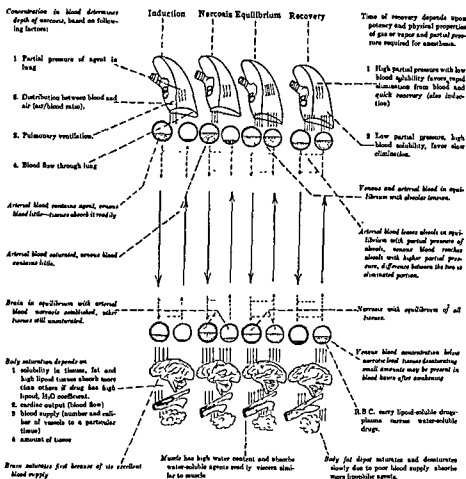
FIG. 5.4. The method of absorption and elimination of gaseous and volatile anesthetic substances is shown. During induction the drug passes into arterial blood and then to tissues. Some tissues absorb a considerable portion. The venous blood returns to the lungs containing little. As soon as equilibrium is established between arterial blood and the brain, narcosis is attained. The venous blood returns to the lungs still containing less than arterial blood because tissues other than brain are not in equilibrium with arterial blood. When complete saturation is attained an equilibrium exists between the venous and arterial blood and all tissues. During recovery the drug leaves the venous blood and passes into the alveoli. The drug in the arterial blood which leaves the lung is in equilibrium with that in the alveoli. The amount which is retained in arterial blood depends upon the air-blood distribution coefficient of the particular agent. During each successive alveolar circulation a proportional distribution occurs between air and blood until the drug is completely eliminated.

sistance to passage of blood through the cerebral vascular system. However, the brain differs in certain respects from other organs in regards to blood flow by possessing a well defined intrinsic con-

trol of the blood vessels within it. Up to a point, blood pressure plays a role in maintaining blood flow. Beyond this, however, the intrinsic regulatory mechanism comes into play and adjusts the

cerebral vascular resistance. This cerebral vascular resistance is influenced by the viscosity of the blood, the intracranial pressure, the calibre of the vessels in the brain, the chemical constituents of the blood and the neurogenic tone of the vessels.

BLOOD BRAIN BARRIER

In addition to cerebral blood flow and vascular resistance, a factor known as the blood *brain barrier* influences the cerebral content of anesthetics. This is thought by some to be an inherent factor of the cerebral cell and capillary *membrane interphase which selectively* resists the passage of substances into the brain. Others feel that no barrier exists and that the selective uptake is a matter of solubility. Direct studies on the rate and ease of the passage of anesthetics across the blood brain barrier are few. If there is any resistance to passage, it must be slight and of little clinical significance because most anesthetics act rapidly. This may be explained by the fact that substances which readily pass the blood brain barrier are generally lipoid soluble. Once the drug passes into the brain it dissolves readily because, relatively speaking, the brain is rich in lipoids.

VENOUS BLOOD TENSION

When *inhalation of an inert gas,* foreign to the body, is first commenced the venous blood level is less than the arterial. On the other hand, the venous blood tension *of a gas which is being eliminated* is higher than the arterial. The rapidity with which the alveolar tension of a foreign gas rises is also influenced, to a great extent, by the *partial pressure* of the anesthetic in the venous blood returning to the lungs from the tissues.

Venous blood returning to the alveoli saturated with the anesthetic facilitates the elevation of the alveolar tension. The venous tension may remain low for a long period of time, particularly if a highly soluble anesthetic, such as ether, is being administered. The venous blood tension is directly influenced by the quantity taken up by the tissues. This depends upon the blood flow through the tissues, such as the muscles, watery organs and the fat depots and the solubility of the drug in these tissues. The muscles, watery organs and adipose tissues constitute the greater portion of the *body weight. Therefore, these consti-*tute the greater portion of the anesthetic absorbing tissues.

RATE OF INDUCTION

The rate of induction of anesthesia, then, corresponds to the rate of buildup of the anesthetic tension in the arterial blood. This depends upon the solubilities of the individual gases. Plotted graphically, the curve representing the *buildup of the concentration in the ar-*terial blood shows a rapid initial rise; then depending upon the displacement of nitrogen and other gases from the lung, a point is reached at which the curve assumes a plateau. The initial rise in the curve represents the buildup of the alveolar tension. The plateau portion of the curve represents the uptake of the anesthetic by the body tissues (Fig. 4.4).

EFFECT OF VARYING INHALED CONCENTRATIONS

The induction period may be shortened by commencing with an inhaled *concentration greater than that neces-*sary to maintain anesthesia. For example, the concentration of ether which is nec-

essary for maintenance of anesthesia is 4 volumes percent or 30 mm. Hg pressure. If induction is commenced with this concentration, considerable time would be required to build up an adequate blood and brain tension because of the high coefficient of solubility of ether. In clinical anesthesiology it is common to commence induction with concentrations of ether as high as 10%. Then, as the alveolar and blood tension increase, the inspired tension is reduced to the maintenance level.

The rate of pulmonary displacement ("washout") of nitrogen depends upon the ratio of effective minute volume respiration to lung volume. When all factors are constant in a given individual, such as cardiac output, minute volume of respiration, lung volume, total mass of body tissue and so on, the differences in the rate of induction with different anesthetics depend upon the differences

in solubility of the anesthetic gas or vapor in the blood and in the body tissues.

SUMMARY OF FACTORS INVOLVED IN ABSORPTION

The factors involved in absorption of gases may be summarized as follows: (1) The tension which is inspired. This establishes the pressure gradient from the outside atmosphere to the inside of the lungs. (2) The tidal exchange. This determines the amount of drug taken into the lung. (3) The functional residual air volume. This determines the degree of mixing and the pressure gradient from alveoli to blood. (4) The area of the diffusion surface. (5) The solubility in blood. (6) The blood flow through the lungs. (7) The blood flow through the brain. (8) Absorption by or penetration into the brain. (9) The solubility in other tissues. (10) The blood flow through other tissues.

ELIMINATION OF INERT VOLATILE ANESTHETICS

After a variable period of time, an equilibrium is established between arterial blood and the tissues. The tension of the gas or vapor in venous blood approaches that of the arterial blood. Approximately 15 minutes elapses before equilibrium is established between venous and arterial blood when cyclopropane is administered. Ether requires much more time. Ether is not only highly soluble in lipoids but is also moderately soluble in water, comparatively speaking. Therefore, it becomes distributed more evenly between the watery and lipoid tissues.

The alveolar tension of a drug is quickly reduced as soon as the administration of the drug is interrupted and room air is inhaled. Any equilibrium

which exists between the blood and the alveolar air is disrupted and the drug begins to diffuse from the venous blood into the alveoli. There is a tendency towards establishment of an equilibrium between the drug which is diffusing into the alveoli and that which remains in the venous blood which is about to leave the lung. This state of equilibrium is never realized, however, because pulmonary ventilation brings in more fresh air. The arterial blood leaves the lung with a concentration of drug which is nearly in equilibrium with that of the alveolar air. Drugs having a large air blood distribution coefficient which require a low partial pressure for anesthesia, such as ether, part with only a small fraction (1/16) of the total dissolved in the blood during
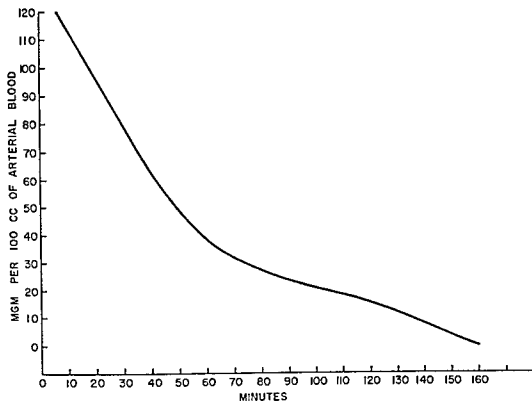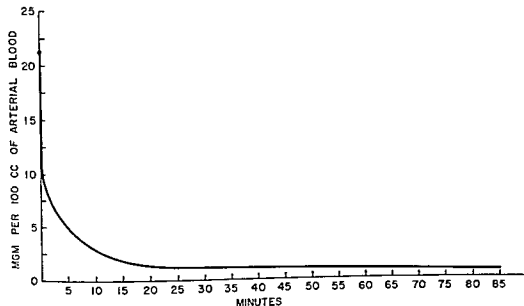
Fig. 6.4. Curves showing comparison of the elimination of
ethyl ether (a) and cyclopropane (b).

each complete circuit to the lung. Re-
covery with this type drug, therefore, is
slow. Drugs which require a high alveo-
lar partial pressure for anesthesia and
which have a low blood solubility, such
as ethylene, are eliminated rapidly.

Tissues which possess a profuse blood
supply and in which the drug is poorly

soluble are not only easily saturated but also easily desaturated. Nervous tissues, particularly the brain, are desaturated sooner than adipose tissues, even though they are both rich in lipoids because they have a more profuse blood supply. Adipose tissues have the poorest blood supply of most soft tissues and are perhaps the last to become desaturated. The elimination of a lipophilic anesthetic from adipose tissues is slow. Long after the other organs are desaturated adipose tissue continues to discharge minute amounts into the venous blood. For example, the greater portion of cyclopropane is eliminated from the blood within 10 minutes. Minute amounts, however, can be detected in venous blood for several hours. This persistant trace is due to the fact that lipoid tissues, since they have both a poor blood supply and a great affinity for the agent, part with it slowly.

The rate of elimination of a substance may be visualized graphically by plotting the concentration in blood at a given moment against time on semilogarithmic paper. The curve plotted from data on the elimination of ethyl ether is a sloping straight line (Fig. 6.4). The curve for chloroform drops rapidly in the first 30 minutes and blends into a straight line. The curve for cyclopropane drops rapidly within 10 minutes and blends into a straight line.

DIFFUSION ANOXIA

At the conclusion of nitrous oxide anesthesia, if air is inhaled, anoxia may result from the rapid outward diffusion of the dissolved nitrous oxide into the alveoli. Nitrous oxide is approximately 30 times more soluble in blood than nitrogen. The outgoing nitrous oxide and the incoming nitrogen, both of which are at high partial pressures could dilute the oxygen to subnormal levels.

DENITROGENATION OF THE BLOOD AND TISSUES

Nitrogen is dissolved in all the tissues of the body. The partial pressure of nitrogen in inspired air at sea level is 79% of one atmosphere, or approximately 600 mm. Hg. The partial pressures in the alveoli, venous blood, arterial blood and tissues are approximately the same. Variations are slight since the gas combines with none of the body constituents. Blood and tissue nitrogen may be replaced by other gases, such as oxygen, helium, nitrous oxide, ethylene and so on. This is accomplished by administering the displacing gas continuously using a semi-closed inhaler with a non-breathing valve (Chap. 3). The exhaled gases pass through one valve while inhaled gases are supplied continuously with fresh displacing gas from a reservoir through another valve. The inhaled tension of nitrogen at the lips and nares is zero. Nitrogen, which forms part of the exhaled gases, is gradually eliminated.

"NITROGEN WASHOUT"

The removal of nitrogen from the lungs and tissues is often called "nitrogen washout." When the lung is normal and there is no maldistribution of gases in the alveoli, nitrogen displacement requires 2½ minutes (Fig. 7.4). The arterial blood, likewise, is rapidly depleted of nitrogen and the nitrogen is replaced by the displacing gas. The tissues, however, desaturate much more slowly. Complete
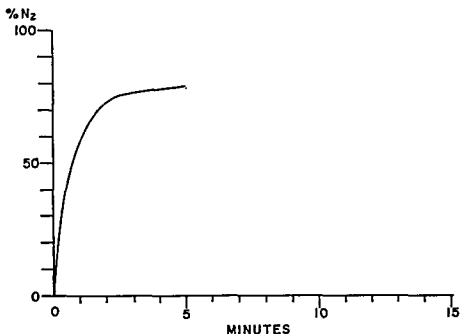
FIG. 7.4. Nitrogen refill time of lung when breathing of air is resumed following inhalation of 100% oxygen. Emptying time and refill time are nearly equal in absence of pulmonary disease (2-3 min.). (See Fig. 8.3, Chap. 3.)

body desaturation requires 7–8 hours. When maldistribution is present, as it is in certain types of pulmonary diseases (emphysema), the nitrogen displacement may require 5 or 10 minutes. Nitrogen emptying time of the lung is used as a basis for pulmonary function tests. The pulmonary nitrogen refill time, likewise, is rapid, requiring 2 to 3 minutes if the lung is normal.

Nitrogen must be eliminated to establish anesthesia with nitrous oxide and ethylene, since these require a high partial pressure in the alveoli and blood to be effective. The nitrogen per se does not interfere with anesthesia. It is objectionable because it dilutes both the anesthetic gas and the oxygen. Elimination of the nitrogen, here again, is accomplished through an expiratory valve of a semi-closed inhaler. After induction of nitrous oxide or ethylene anesthesia with a non-rebreathing valve the nitrogen is completely eliminated from the alveoli

and blood and the concentration is nearly zero. Gradually, during maintenance, there is an interchange between the nitrogen dissolved in the tissues and the anesthetic gas in the blood. If the semi-closed system has been converted to a closed one, nitrogen begins to accumulate in the inhaler. Therefore, a periodic "washout" is necessary to prevent dilution of the gases with nitrogen (Fig. 8.4).

TISSUE NITROGEN

The bowel distension in intestinal obstruction is due largely to the accumulation of nitrogen within the lumen. Inhalation of 100% oxygen through a semi-closed system establishes a gradient for nitrogen from tissues to blood to alveoli to outside air. The gas is gradually eliminated from tissues and replaced by oxygen. The nitrogen from the bowel then passes into the tissues and the distension is reduced. The removal of air from the cerebral ventricles following encephalog-
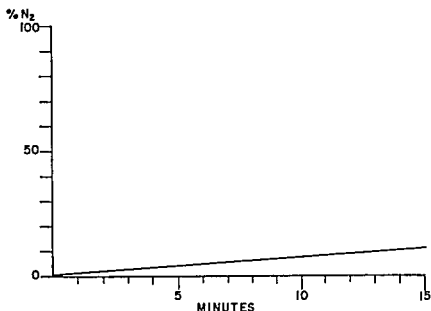
FIG 8.4. Accumulation of excreted tissue nitrogen in a closed inhaler after previous pulmonary nitrogen washout using 100% oxygen administered with a semi-closed inhaler. Oxygen is being added to maintain a constant volume in the system.

raphy, or other air contrast studies, may be also accelerated in the same manner. A high partial pressure of oxygen in tissues is desirable for treating anaerobic infections. This is also obtained by replacement of nitrogen by oxygen by inhalation of oxygen rich mixtures using a semi-closed inhaler.

NITROGEN NARCOSIS

Divers submerged at great depths who are exposed to air pressures of four or five atmospheres frequently become disoriented. It has been established that this is due to the narcotic effect of the increased quantity of nitrogen which dissolves in the brain. The amount which dissolves in plasma is in proportion to the pressure. Besides, nitrogen is approximately five times more soluble in lipoids than in water. The brain and adipose tissues, therefore, take up a greater amount than non-lipoid containing cells (see Chap. 6). Behnke found

that the substitution of helium for the nitrogen in the inhaled gases minimized the narcotic effects. Helium is not only inert but is the least soluble of the elemental gases. Helium has a lower oil/water partition coefficient than nitrogen. Less helium dissolves in, not only the aqueous, but also the lipoid portions of the cell at the increased pressure to which the diver is exposed.

DECOMPRESSION

A sudden transition from a high to a low environmental pressure causes a rapid release of dissolved gases in blood and tissues referred to as *aeroembolism.* Desaturation of tissues of persons who have been exposed to atmospheres of high pressures must be slow. Usually, the pressure is decreased at increments of one-half at intervals of one hour. Unless this is done innumerable small bubbles form which act as emboli and which obstruct the capillaries and cause in-

jury and death of cells. Nitrogen, which is the predominating gas, causes most of the difficulties. However, oxygen also causes persistent emboli. The more obese the subject is, the greater the total amount of gases which are absorbed and the larger the decompression response (see Air Emboli page 148).

PULMONARY COLLAPSE DUE TO ABSORPTION OF GASES

Should the bronchus serving a lung lobule be occluded so that the air and other gases are trapped in the alveoli and the blood supply remains intact and perfusion still continues through this unventilated pulmonary tissue, the lobule will ultimately collapse. This is due to the absorption of the gas from the alveoli of this lobule. The rapidity and completeness of collapse depends upon the nature of the gas. Gases which have (1) a low water solubility, (2) those which do not combine chemically with constituents of the blood or (3) those which are normally present in a high concentration in the blood (nitrogen) are absorbed slowly. Coryllos and his associates studied the absorption of oxygen, nitrogen, helium and various anesthetic gases and vapors from the lungs of dogs with occluded bronchi with an intact blood supply. *Nitrogen disappears very slowly* (16 hours). This presumably is due to the fact that the pressure gradient of nitrogen across the alveolar membrane is low since the tension of nitrogen in the blood is about the same as that of the alveoli. Helium disappears more slowly than nitrogen (26 hours) probably because of its low solubility in plasma. Oxygen, carbon dioxide, ether, chloroform, nitrous oxide and other inhalational anesthetic *gases and vapors* are quickly absorbed (in less than ¼ hour)

because they either combine with constituents of blood or they are normally not present in blood but soluble in it. This rapid deflation of the lung lobule is followed by a collapse of the alveoli. The importance of this phenomenon as the causative factor of atelectasis is obvious. It must be emphasized that atelectasis is not prevented by the inhalation of slowly absorbed gases (helium). It is merely delayed. If an obstruction to a bronchus is not relieved the lung will ultimately collapse regardless of the slowness of absorption of the gas. Besides, *the slowly diffusing gas must be trapped in the alveoli before the occlusion of the bronchus occurs* if it is to be effective in delaying the collapse.

USE OF INERT GASES FOR INHALATION THERAPY

Helium is sometimes added to inhaled mixtures in cases of respiratory obstruction to decrease respiratory effort. The underlying rationale is that, since helium is light, it diffuses in and out of the bronchi and alveoli with greater ease than nitrogen (Graham's Law). In addition, the degree of turbulence is decreased because of the lower viscosity. How important a role the viscosity of helium plays is debatable since the difference between it and air is so slight.

Then, also, helium may lighten the respiratory load. A mixture of 80% helium and 20% oxygen weighs approximately ⅓ as much as an equivalent volume of air. Thus, theoretically, ⅓ the effort must be made to inhale this mixture than is necessary to inhale air. This is of theoretical advantage in reducing the respiratory effort.

Helium is also used as a quenching agent to reduce flammability of anesthetic mixtures (see Chap. 26).

AIR EMBOLISM

The rapid decrease of pressure of the inhaled atmosphere results in the formation of nitrogen bubbles in the tissues and blood referred to as *aeroembolism*. These bubbles are *endogenous*, that is, they originate from the dissolved gases. Air may inadvertently be introduced into the vascular system giving rise to the phenomenon called *air embolism*. These bubbles are *exogenous*, that is, they are introduced from without by injection and aspiration.

Air embolism is not uncommon. Its sequelae are serious and often fatal. Aeroembolism is more frequent after deep sea diving than in high altitude flying because the number of atmospheres of pressure differences involved in diving are far greater than in flying (from 4 or 5 in diving to 1 to ⅓ or ¾ in flying).

Air embolism may result from aspiration of air into the great veins during surgical procedures, particularly in operations of the upper extremities. A negative pressure exists in the veins in these areas. If a vein is inadvertently opened, air may be aspirated into it during inspiration. The accidental intravenous injection of air while transfusions are being given under pressure is a preventable cause of air emboli. Air may be aspirated into infusion tubing during intravenous therapy at connections which are loose. Considerable study has been directed toward the cause and prevention of air emboli and the manner in which they cause death. Presumably, they cause death by mechanical blockage.

AIR IN THE PULMONARY AND SYSTEMIC CIRCULATION

It has been shown that gases injected into the pulmonary veins of cats in quantities exceeding 0.5 ml. per pound of body weight forms bubbles which pass into the left side of the heart and lodge in the coronary vessels and the brain. Death, apparently, is the result of ischemia of the myocardium and brain because the bubbles so formed persist. Carbon dioxide in volumes up to 2 ml. per pound of body weight also forms bubbles which pass into the coronary vessels, but does not cause death because the gas is absorbed almost completely by the blood within 15 to 20 seconds. The animal survives the injection of this gas. The carbon dioxide apparently combines with the amino groups of the protein in the blood, by virtue of their basic qualities, to form carbamino compounds. Nitrogen combines with none of the constituents of plasma. The bubbles persist for a long time.

Air, entering the systemic veins, passes into the venae cavae and then to the right heart where it is churned into a foam which eventually lodges in the pulmonary capillary bed in the form of multiple, small emboli. A churning sound may be heard over the pericardium when air is present in the heart (mill wheel murmur). Apparently little or no air reaches the left ventricle. The air must pass into the pulmonary vein for it to pass into the left side of the heart and the coronary vessels and aorta. The "head-up" position is undesirable because it favors accumulation of the air bubbles in the arch of the aorta and subsequent passage of bubbles into the cerebral vessels where they cause cerebral emboli.

PERSISTENCE OF AIR EMBOLI

The persistence and slow disappearance of air emboli have been explained on a physical-chemical basis. A gas churned with a colloidal solution forms

a foam which consists of a gel-like plastic film surrounding a gaseous phase. The superficial viscosity of this film has been shown to be over a thousand times greater than that of water. The viscosity of the film depends upon the nature of the colloidal solution. Since blood contains protein and is, therefore, a colloidal solution, it forms such protein films. An air embolus, therefore, is nothing more than an air bubble surrounded by a thin, tenacious protein film. Langmuir studied the viscosity and elasticity of such protein films and has found them to be comparatively resistant, tough membranes. He suggested that the protein in the films is denatured and that the film persists because the alteration in the protein causes the film to be much tougher than it would be with the natural protein. Neither nitrogen nor oxygen combine with the protein. They are not able to quickly penetrate the membrane. The embolus, therefore, persists for a long time in tissues.

INTRAVENOUS OXYGEN

The intravenous injection of oxygen for the relief of anoxemia is suggested and attempted from time to time. Not only is this procedure of little value therapeutically, but it is also dangerous. Oxygen forms emboli as readily as does nitrogen or air. Such emboli are nearly as persistent as those formed from air or nitrogen. However, since oxygen is utilized by tissues, the bubbles which form do not persist for as long a time in blood, particularly if injected slowly. Therefore, limited amounts of oxygen may be injected without apparent harm. In dogs the lethal dose of oxygen, when injected into the systemic veins, is 2 to 3 cc. per kilogram per minute.

Marked respiratory changes and a decrease in blood pressure develop in dogs given oxygen rapidly intravenously. Oxygen, at the rate of 0.35 to 2.3 cc. per kilogram per minute, not only does not correct any existing anoxemia but actually enhances it.

GASES AT INCREASED PRESSURE

The clinical administration of anesthetic gases at increased pressure was first suggested and tried by Paul Bert in 1878. By using pressures greater than atmospheric it is theoretically possible, when using oxygen poor mixtures, to obtain oxygen tensions in blood equivalent to those obtained by inhaling air at ordinary atmospheric pressure. Nitrous oxide, for example, requires a high inhaled, alveolar tension to be an effective anesthetic. Sub-oxygenation frequently results. However, if a mixture of 84% nitrous oxide and 16% oxygen, which at ordinary atmospheric pressure is physiologically inadequate as far as the oxygen tension is concerned, is administered at 1.2 at-

mospheres pressure, the partial pressure of the inhaled oxygen, according to Dalton's Law, will be 152 mm. Hg. Oxygen in air at 760 mm. Hg exerts the same pressure—152 mm. Hg. Since the amount of a gas which dissolves in a liquid is proportional to the partial pressure, the amount of oxygen which dissolves in blood at this pressure is equivalent to that which dissolves in plasma at atmospheric pressure. Theoretically, adequate oxygenation may thus be maintained with drugs such as nitrous oxide or ethylene which require high partial pressures for effective anesthesia using this technique. Not only does more oxygen dissolve but more of the anesthetic drug

also. Ordinarily, nitrous oxide is impotent. Lethal quantities cannot dissolve in blood if inhaled at atmospheric pressure with 20% oxygen. The gas must be given under increased pressure for lethal amounts to dissolve in plasma. Nitrous oxide administered at 3 atmospheres pressure, simultaneously with a physiologically adequate oxygen tension, is lethal to mice. The clinical administration of a nitrous oxide-oxygen mixture varying from 85% N_2O–15% O_2 to 88% N_2O–12% O_2 at a pressure averaging 10–15 mm. Hg above atmospheric was ineffective in materially increasing the arterial oxygen tension according to Cullen and his associates. Pressures higher than these are generally not safe in clinical anesthesia because of the possible danger of rupture of the lungs.

Carbon Dioxide Absorption

DISPOSAL OF CARBON DIOXIDE FROM INHALERS

CARBON DIOXIDE must be disposed of completely from closed inhalers for safe inhalational anesthesia. This is accomplished by a "washout" using high gas flow rates in a semi-closed system or by chemical filtration. Both methods are extensively used. The chemical filtration technique permits complete enclosure and rebreathing of the gases and, therefore, possesses obvious advantages over the semi-closed (Chap. 4). The terms *complete rebreathing, the closed system,* and *carbon dioxide absorption technique* are used to designate this method of inhalation anesthesia. The rebreathing technique requires a leakproof inhaler which is air tight with the patient's upper respiratory tract.

HISTORY OF CARBON DIOXIDE ABSORPTION

Scheele (1777) probably first used carbon dioxide absorption in an experimental manner on living things. He placed bees and a small amount of honey in a glass jar inverted over lime water. The water rose into the jar to replace the oxygen consumed by the bees. The eliminated carbon dioxide was absorbed by the lime water. In 1789 Antoine Lavoisier, while performing his experiments on metabolism, showed that guinea pigs placed in a chamber eliminated carbon

dioxide. He absorbed the carbon dioxide with caustic soda. In 1847 Regnault and Reiset applied the same principle to larger animals. Dogs were kept alive in a closed chamber for several days. Oxygen was added and carbon dioxide was absorbed with lime. In 1850 John Snow inhaled chloroform vapors with a closed apparatus containing potassium hydroxide to absorb carbon dioxide. He also used carbon dioxide absorption for anesthesia in animals. He demonstrated that carbon dioxide output is decreased during chloroform and ether anesthesia. In 1853 Schwann prepared an air tight rebreathing apparatus for mine rescue work. This consisted of an inhaler containing alkali for absorbing carbon dioxide and an external source of oxygen. *This is probably the first apparatus of a completely closed type designed for rebreathing to control the gaseous exchange in man.* Alfred Coleman (about 1871) a dentist, designed a to and fro unit with which he administered nitrous oxide to dental patients. He used slaked lime as the absorbent. Benedict, in 1909, described the use of the closed system using soda lime as the absorbent for carbon dioxide in his important researches in metabolism in man. Dennis Jackson, in 1915, used the closed system for inhalation anesthesia with nitrous oxide in laboratory animals and also to a limited extent in man. In his laboratory
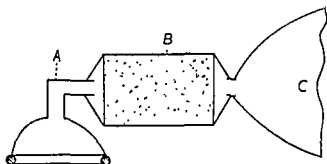
FIG. 1.5. The to and fro unit composed of a mask (A) canister (B) and rebreathing bag (C). The gases pass over the absorbent during inspiration as well as expiration.

work a pump forced the exhaled gases through aqueous solutions of alkalis which absorbed the carbon dioxide.

Brown and Foregger in 1909 and later Brindley and Foregger in 1923 experimented with sodium peroxide in submarines. Sodium peroxide reacts with water to form sodium hydroxide. The latter absorbs carbon dioxide. In addition, oxygen is also liberated but not in proportion to the amount of carbon dioxide absorbed. Ralph M. Waters, taking a cue from Jackson, applied the principle of chemical absorption of carbon dioxide to clinical anesthesia. His early attempts were patterned after the laboratory experiments of Jackson in which he employed a closed circle arrangement consisting of an aqueous alkaline solution through which the exhaled gases were forced mechanically. Later, the mechanical device was discarded in favor of a circle type filter. Still later, he abandoned this and adopted a direct or to and fro system which now bears his name. In 1929 Brian Sword devised the circle filter which was in many respects similar to the filter used on man by Jackson.

The rebreathing technique of anesthesia was slow to gain popularity. Waters first published his reports in 1923. For at least 10 years afterward few anesthetists adopted the technique. The

introduction of the relatively expensive drug cyclopropane (1933) and the increased interest of physicians in the practice of anesthesiology were responsible for the sudden, renewed interest in the carbon dioxide absorption method of anesthesia.
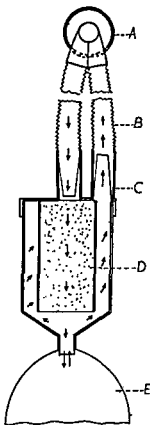
FIG. 2.5. The circle filter is a unit composed of a mask (A) and two breathing tubes (B) which are corrugated to prevent kinking. These are connected to valves (C). One valve communicates with the inlet of the canister (D) and the other with the outlet. The flow of gases through the absorbent is unidirectional and occurs during expiration. If the valves are reversed the gases pass over the absorbent during inspiration. (E) is a rebreathing bag used as a reservoir.

TYPES OF REBREATHING APPARATUS

Two types of rebreathing appliances are in use today, the *to and fro* (Waters canister) type and the *circle* system. The To and Fro unit is composed of a cylindrical canister filled with a chemical absorbent, a face piece attached to one end of the canister and a rebreathing bag attached to the other (Fig. 1.5). In the Waters canister, exhaled gases pass from the face piece through the canister filled with absorbent to the breathing bag. During inhalation the gases reverse their flow and pass back into the face piece. In the circle type (Fig. 2.5), a canister is connected to a face mask by means of a Y piece and two corrugated kinkless tubes. Valves are interposed in the system, at the inlet and at the outlet of the canister, in order to establish a unidirectional flow and separate the inspiratory gases from the expiratory. A breathing bag introduced at a convenient point in the circuit, usually at the canister outlet, acts as a reservoir for the respired gases.

FLOW OF GASES IN EACH TYPE OF UNIT

The gases in the to and fro unit are in constant motion, except for a brief interval during the expiratory pause when they become stationary before reversing their flow (Fig. 3.5). During part of the expiratory pause gases are coming to rest. Each respiration of an adult breathing twenty times per minute occupies approximately three seconds provided breathing is regular and inspiration equals expiration. Inspiration occupies a somewhat longer time interval than expiration, as a rule. The inter-respiratory pause comes at the end of expiration. It may occupy up to 0.3 of a second. These
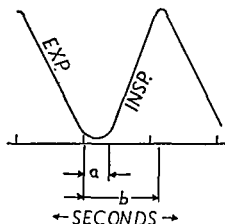
FIG. 3.5. Shows a comparison of the time interval during which the gases remain at rest in the circle and to and fro units. In the to and fro the interval is brief and lasts only during a part of the pause which occurs at the end of expiration (a). In the circle filter the gases move through the absorbent during one phase of respiration. In the arrangement in Fig. 2.5, they pass over the absorbent during expiration and remain at rest and in contact with the absorbent during inspiration. This time interval is represented by (b).

figures, of course, may vary from patient to patient and from moment to moment even in the same patient. In any event, the period during which the gases are at rest is brief. In the circle filter the gases move into the canister during expiration. In view of the unidirectional flow they come to rest and remain at rest until the next inspiration. During inspiration filtered gases are drawn, not from the canister but, from the bag into the mask. At the next expiration the newly expired tidal volume of gases forces the gases from the previous expiration farther into the canister, if the canister is large, or out of it into the bag if it is small. The gases remain at rest during the expiratory pause and during all of inspiration. This is a period of at least 1.5 seconds. Longer contact with the absorbent occurs in the circle filter ($\pm$ 1.5 sec.) than in the To and Fro ($\pm$ 0.3 sec.).

CHEMISTRY OF ABSORPTION

ANHYDRIDES OF ACIDS AND BASES

Certain gaseous non-metal oxides, as for example, carbon dioxide, sulphur dioxide and hydrogen sulphide form *acids* in the presence of water. These oxides are anhydrides of acids. They, therefore, react with the oxides, peroxides and hydroxides of many metals and with certain organic amines. Metal oxides are anhydrides of bases. They, therefore, combine with water to form *hydroxides* or bases. Hydroxides actively combine with acidic gases. The ease with which carbon dioxide and other acidic gases are absorbed depends upon the activity

TABLE I.5

Cs
Rb
K
Na
Li
Ba
Sr
Ca
Mg

Activity series of alkaline and alkaline earth metals.

of the metal forming the oxides or hydroxides. This is determined by its position in the electromotive series (Table I.5).

ALKALI METALS

The most active hydroxides are those of the alkali metals since these occupy the uppermost position in the electromotive or activity series. In order of declining activity of the alkali metals are caesium, rubidium, potassium, sodium and lithium. Sodium hydroxide is the most extensively used hydroxide of the alkaline metals because it is highly active, abundant and relatively inexpensive. Potassium hydroxide, though more

active, is used to a lesser extent because it is less abundant and more expensive. Lithium hydroxide has been advocated for absorption of acidic gases but it has not proved feasible for anesthesia. The other metals are less abundant and, therefore, are not used.

ALKALINE EARTH METALS

Next in activity to the alkaline metals are the alkaline earth metals. The order of activity is barium, strontium, calcium and magnesium (Table I.5). Of these, barium and calcium hydroxides are the most serviceable. Strontium is more active than calcium but less abundant. Magnesium hydroxide is not sufficiently active to effectively absorb acidic gases. The hydroxides of zinc, iron and copper and other metals are not sufficiently active to completely absorb carbon dioxide quantitatively in anesthetic appliances.

NEUTRALIZATION

The reaction of absorption of carbon dioxide (or other acidic gases) by a hydroxide is a neutralization. Carbon dioxide first combines with water to form carbonic acid.

$$CO_2 + H_2O \rightarrow H_2CO_3$$
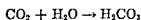
The acid is neutralized by the base only if both are ionized. *Neutralization* is the union of hydrogen ions with hydroxyl ions to form undissociated molecules of water. The carbonic acid, in the presence of water, dissociates into hydrogen and carbonate ions.

$$H_2CO_3 \rightarrow 2H^+ + CO_4''$$
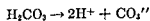
The base yields hydroxyl ions. Once hydrogen and hydroxyl ions unite to form water the union is firm and the reaction

is irreversible. No significant dissociation occurs because only one water molecule in 10,000,000 dissociates into hydrogen and hydroxyl ions at room temperature (25°C.). The reaction of neutralization is exothermic; therefore, heat is evolved. This heat, referred to as the heat of neutralization, is a constant quantity and amounts to 13,700 calories for each mole (18 grams) of water formed. The caloric output during neutralization may vary several hundred calories per mole one way or the other depending upon the degree of ionization of the acids and bases which interact. The metallic ion (cation) forms a salt with the acidic (anion). In the case of carbonic acid the salts formed are called carbonates.

EFFECT OF IONIZATION OF ACIDS AND BASES ON NEUTRALIZATION

The dissociation of a substance into ions is only partial. Some of it remains undissociated. A substance which dissociates almost completely into its respective ions is referred to as being *highly ionized*. Highly ionized acids and bases are called *strong* acids and bases. The hydroxides of the alkali and alkaline earth metals are strong bases because they are highly ionized in aqueous solutions. Carbonic acid, however, is a weak acid because it feebly dissociates into hydogen and carbonate ions (0.0017 at 18°C.). The quantity of a weak acid required to neutralize a mole of strong base, or vice versa, a strong acid and a weak base, is the same as if both were strong and highly ionized. Inasmuch as only a small portion of the total of a strong acid or a base is unionized, neutralization occurs promptly and with ease. A strong base added to a weak acid is not neutralized as readily, even

though the reaction goes on to completion, due to the effects of partial ionization of the acid. Only the hydrogen ions interact with the hydroxyl ions. As quickly as the hydrogen ions are converted to water, the unionized portions of the acid are ionized to re-establish and maintain the equilibrium which exists between the undissociated and the ionized substances. As rapidly as these hydrogen ions form they in turn combine with hydroxyl ions to form water. Ultimately all of the unionized acid is ionized and neutralized by the alkali. Some of the liberated heat is used for the ionization of the weak acid. The heat of neutralization is less when dealing with weak acids or bases than when the neutralization is between a strong acid and a strong base. The heat of neutralization of a weak acid, such as carbonic acid, by sodium hydroxide is approximately 13,400 calories per mole of water formed.

SOLUBILITY OF ALKALIS

The hydroxides of sodium and potassium are both very soluble in water. In fact, they have such an affinity for water that they form thick gelatinous solutions when they are exposed to moist air. In other words, they are *hygroscopic*. Sodium hydroxide dissolves in its own weight of water. A saturated solution of sodium hydroxide at 25°C. has a strength of approximately 20 molar.

The alkaline earth hydroxides are less soluble than those of the alkali metals. One gram of barium hydroxide dissolves in 11.6 ml. of water at 25°C. One gram of calcium hydroxide dissolves in 630 ml. of water at 25°C. Thus, barium hydroxide is more effective as a neutralizing agent because it is both more soluble and more active. Ionization of barium hydroxide is almost as great as that of

sodium hydroxide (0.63% vs. 0.69% at 18°C. for a 1.0 N solution). Aqueous suspensions of barium, calcium and magnesium hydroxides are referred to as "milk of barium," "milk of lime," and "milk of magnesia" respectively. If a suspension of each of the four alkaline earth hydroxides is permitted to settle and the supernatant liquid overlying the precipitate is drawn off, a saturated solution of the respective bases is obtained. Even though these hydroxides are poorly soluble, they are strongly basic because they are highly ionized. Barium hydroxide is approximately 0.92% ionized in dilute solution. They are feebly caustic compared to sodium and potassium hydroxide because of the diluteness of the solutions formed. These solutions may be used to detect the presence of carbon dioxide in air or mixtures of other gases. This they do by forming carbonates, which are white powders. All four carbonates are almost totally insoluble and, thus, even the slightest trace of carbon dioxide yields a milky cloud in the clear solution of the hydroxide. The carbonates of the alkali metals are soluble and cannot be used for this purpose.

BICARBONATE FORMATION

The end products of the neutralization of carbon dioxide by an alkali are, then, water and the carbonate of the respective metallic hydroxide involved. An excess of carbonic acid may react further with a carbonate to form a bicarbonate. Sodium bicarbonate and carbonic acid react to form sodium bicarbonate as follows:

$$Na_2CO_3 + H_2CO_3 \rightarrow 2\ NaHCO_3$$
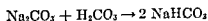
Calcium and barium also form bicarbonates in the presence of excess carbonic acid. During clinical anesthesia bicarbonates may form in parts of the canister where complete conversion of the alkali to carbonates has occurred. However, the efficiency of the entire charge of absorbent decreases before all of the alkali is exhausted and bicarbonate formation begins. More than the tolerable amount of carbon dioxide filters through before appreciable bicarbonate formation occurs.

SOLUBILITY OF CARBONATES

Potassium, sodium and lithium carbonates are water soluble salts. Sodium carbonate is the most important of the alkali carbonates from the standpoint of anesthesiology. It forms two hydrates, a decahydrate ($Na_2CO_3 \cdot 10H_2O$) and also a monohydrate ($Na_2CO_3 \cdot H_2O$). Barium carbonate is less soluble than calcium carbonate and calcium carbonate less than that of magnesium. Pure crystalline calcium carbonate occurs in a number of forms, one of which is marble. Although not caustic, soluble carbonates of alkali metals form alkaline solutions when dissolved in water due to hydrolysis, since they are salts of weak acids and strong bases. Such salts are highly ionized in aqueous solutions. The ions of water in a solution of a soluble carbonate interact with the ions of the salt and tend to form carbonic acid, which is a weak acid and sodium hydroxide which is a strong base.

DECOMPOSITION OF CARBONATES

Carbonates of alkaline metals are relatively stable and decompose only when heated to unusually high temperatures. Carbonates of the alkaline earth metals, if heated strongly, dissociate into the oxide of the metal and carbon dioxide.

$$CaCO_3 \rightarrow CaO + CO_2 \uparrow$$

Calcium carbonate is abundantly distributed in the earth in the form of limestone. Limestone is the source of most calcium products. Limestone heated at 825°C. decomposes to calcium oxide and carbon dioxide. The oxides of alkali and alkaline earth metals readily combine with water to form hydroxides.

$$CaO + H_2O \rightarrow Ca(OH)_2$$
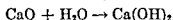
Heat is evolved in the reaction. Calcium oxide, commonly known as *quicklime*, is converted by water or by the moisture of the air to calcium hydroxide *(slaked lime)*. Alkaline metal oxides and alkaline earth metal oxides, *in the presence of* traces of moisture, react with carbon dioxide to form carbonates. This reaction is accompanied by the evolution of considerable heat—more than would be evolved if the hydroxide were the absorbent. *The total heat evolved, theoretically speaking, is equal to the sum* of that required to form the hydroxide from the oxide by the addition of water, the heat of solution of the hydroxide, and the heat of neutralization of the re-*sulting hydroxide by carbonic acid.*

METALLIC PEROXIDES

The oxides of many metals are converted to peroxides when heated in air or oxygen. Barium oxide, for example, *heated at red heat in air is converted to* barium peroxide (BaO_2).

$$2 BaO + O_2 \rightarrow 2 BaO_2$$

These metallic peroxides react with water to form hydroxides and liberate oxygen. They also react with carbonic acid, in which case they yield oxygen, water and carbonates. The alkaline metal peroxides are active enough to absorb carbon dioxide. Sodium peroxide was used experimentally by Brindley and Foregger in closed inhalers to absorb

exhaled carbon dioxide. It also acts as a source of oxygen. The reaction is as follows:

$$2 Na_2O_2 + 2 H_2O \rightarrow 4 NaOH + O_2 \uparrow$$
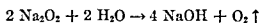
HEAT OF SOLUTION OF BASES

Most chemical substances either absorb or liberate heat when they dissolve in water. When the hydroxides dissolve in water the reaction is exothermic. This heat is known as the *heat of solution*. Hydroxides, particularly those of alkaline metals liberate considerable heat when they dissolve in water. The high heat of solution, the markedly hygroscopic properties and the caustic nature of the hydroxides of the alkaline metals limit their usefulness for carbon dioxide absorption in rebreathing appliances.

AVAILABLE ABSORBENTS FOR CARBON DIOXIDE

The first absorbents used for carbon dioxide absorption were aqueous solutions of sodium hydroxide, slaked lime or mixtures of calcium and sodium hydroxide. Aqueous solutions of alkalis are impractical, difficult to manage and dangerous for clinical use because of their caustic nature. Sticks, flakes and crystals of the hydroxides of potassium, sodium and lithium have been used as absorbents. They absorb moisture from the patient's lungs and, thus, form caustic solutions which are hazardous. Also, they become coated with carbonates and cease to absorb effectively after a short period of use.

An absorbent known as *shell natron* has been used in oxygen tents and for clinical research. This consists of sodium hydroxide molded into the form of "sea shells." Laboratory absorption of carbon dioxide is often carried out with asbestos impregnated with sodium hydroxide

(Ascarite). Mixtures of barium and calcium hydroxide are effective absorbents and are used for anesthesia. These are described in detail later in this chapter. The hydroxides of the metals below the alkaline earth metals in the electromotive series are insoluble or feebly basic and of no value. Zinc and aluminum react with sodium hydroxide to form zincates and aluminates. These are alkaline substances capable of absorbing carbon dioxide. However, they are not as efficient and as easily handled as the hydroxides of the alkali and alkaline earth metals. Ammonia will absorb carbon dioxide but is too feeble and volatile a base to be effective. Organic amines have been investigated as possibilities as absorbents. The results, thus far, have been disappointing. Adsorption with anion exchange resins derived from polymerization of phenols and other organic compounds has been investigated as a possibility for absorbing carbon dioxide but also has been found to be impractical. Removal is not quantitative and, therefore, incomplete. Besides, resistance due to smallness of the particles is too great. Adsorption of carbon dioxide by agents such as silica and activated charcoal, likewise, has not proved feasible from a clinical standpoint.

DEVELOPMENT OF SODA LIME

Early in the search for a satisfactory absorbent, calcium hydroxide was used alone as an absorbent, since it was abundant, inexpensive and easily handled. Black, Lavoisier, Snow and others used ordinary slaked lime in their experiments. It was soon apparent, however, that absorption using slaked lime was not efficient. The observation was soon made that absorption was more effective when sodium hydroxide was

added to lime. Mixtures of sodium and calcium hydroxide were then developed which were referred to as *soda lime.* *Soda lime is a mixture of several chemicals and not a specific compound.*

Early in the use of soda lime these mixtures consisted of equal portions of sodium hydroxide and lime. However, these mixtures are not satisfactory for clinical use. The hygroscopic nature and the high heat of solution of sodium hydroxide causes excessive heating and "caking." During World War I the need arose for an effective alkaline absorbent for use in gas masks when poison gases were introduced as a tactical weapon. Wilson and other U. S. Army engineers of the chemical warfare service developed a grade of soda lime which was a satisfactory absorbent for acidic gases for gas masks. Several years after the war (1923) Waters introduced carbon dioxide absorption into anesthesia using the soda lime developed by Wilson and his associates.

SODA LIME FOR ANESTHESIA

Special preparations and precautions are necessary to prepare a soda lime mixture satisfactory for clinical use. Ingredients must be of a good grade and of reasonable purity. The calcium hydroxide must be prepared from a high grade of calcium oxide. It must be free from contamination by the oxides of magnesium, aluminum and other metals since the latter decrease the efficiency of the final product. Wilson found that the sodium hydroxide content of soda lime could be reduced to as low as 5% before any significant decrease in absorptive capacity occurred. Specimens containing more than 5% sodium hydroxide, although more efficient, caused excessive heating and "caking." The calcium hy-

droxide is the mainstay of the absorption and performs the bulk of the work. In England absorbents of higher sodium hydroxide contents are used.

The soda lime mixture, although easy to mold into any desired shape or form, crumbles and pulverizes into objectionable dusts. Wilson added silica to the mixture to obviate dust formation and preserve the shape of the granule and impart hardness. Silica (SiO_2 silicon dioxide) is the anhydride of silicic acid. Calcium hydroxide and sodium hydroxide react with it to form calcium silicate ($CaSiO_3$) and sodium silicate (Na_2SiO_3). These silicates are the salts of silicic acid. Silicates of *calcium* are hard, glasslike substances. Sodium silicate is water soluble and forms a gelatinous hydrate. *The greater the quantity of silica added*, the greater degree of hardness of the granules. Unfortunately, the absorptive power *decreases with the hardness. As* a rule the absorption efficiency of soda lime varies inversely as its hardness. Present day soda limes used for anesthesia have little or no added silicates in order to avoid this decrease in efficiency.

The ingredients are thoroughly mixed and the mass is fused into sheets which are allowed to harden. These are then *fragmented into miscellaneous sizes.* Later they are graded with a standard screen into sizes which vary anywhere *from 4 to 20 mesh. The mesh of a screen* is determined by the number of openings per inch of screen. Thus, a four *mesh screen has four quarter inch square* openings per inch; an eight mesh eight eighth inch openings, a sixteen mesh sixteen and so on.

SIZE OF GRANULES

The size of the granules is an important factor because the efficiency of absorption depends upon the size of the surface presented to the reacting gases. The smaller the granule, the more efficient the absorption because a greater surface is presented to the ambient gases per unit of weight of absorbent. Soda lime used for anesthesia is a blend of granules varying from sizes of 4 to 8 mesh. The larger 4 mesh comprises 6–8% of the total. The bulk of the mixture consists of 6 mesh lime. The size of the granules also determines the amount of turbulence which develops and the volume of gases which fits in between the granules. This gas space in between the granules is important and will be discussed later in the chapter. Fine mesh soda lime 20 to 40 mesh is employed in basal metabolism machines equipped with blowers to force the gas through the system.

MOISTURE CONTENT

Wilson and *his* associates noted that soda lime was ineffective in gas masks unless moisture was incorporated in the granule. A certain amount of moisture was necessary to promote absorption. Two types of soda lime were thus developed, the "wet" *or high moisture and* the "dry" or low moisture. High moisture soda lime contains a variable quantity of water. *Neither sodium hydroxide nor calcium hydroxide forms hydrates. The* moisture in soda lime, therefore, *is not present in definite proportions. The* water is probably present as a thin film on the surfaces of the particles. Anhydrous soda lime exposed to a humid atmosphere absorbs some water. However, since the sodium hydroxide content is approximately 5%, the absorption of moisture is not remarkable. Moisture must be deliberately added to assure a high water content. Calcium hydroxide *is not* hygroscopic. Moist soda lime, on the

a dry atmosphere. Thus, the moisture content of soda lime is quite variable and depends, to a large extent, upon the water content of the atmosphere to which it is exposed. The moisture in soda lime granules is not visible when the content is less than 20%. If greater than 20% the granules appear and feel wet. While there may be no appreciable difference from a clinical standpoint in the neutralizing ability of soda lime containing 10%, 15% and 20% water, there are detectable differences in laboratory studies. Neutralization becomes progressively more effective as the moisture content increases. The greater the sodium hydroxide content, the greater its tendency to absorb water from the atmosphere. Absorption of weakly acidic substances does not proceed satisfactorily when low moisture soda limes are used in closed inhalation appliances, even though exhaled moisture is present and the gases are humidified. The moisture is necessary to form carbonic acid from carbon dioxide and for ionization of the acid. The moisture must be incorporated in the absorbent. In addition, it is necessary to facilitate the interaction of sodium carbonate with the less active but more abundant calcium hydroxide in the granules to reform sodium hydroxide. This aspect of absorption will be discussed further on. Consequently, water must be added to soda lime to promote effective absorption.

SOURCES OF WATER IN THE INHALER

Water accumulates in the inhaler and condenses in the bag and in the tubes. The greater portion of this condensed water is derived from the reaction of neutralization. Some is obtained from the pa-

tient's lungs but the quantity is relatively little, however. In spite of the fact that moisture is present in the exhaled gases, that water vapor is liberated from the reaction and that the system is entirely closed, absorption is not effective when low moisture soda lime is used. The water must be incorporated into and be a physical part of the soda lime granule. Moisture does not facilitate absorption in the vapor state. Dry gases are freed of carbon dioxide provided the moisture content of soda lime is high.

EXHAUSTED ABSORBENT

Granules of exhausted soda lime are harder than those of the fresh absorbent because they consist almost wholly of calcium carbonate. This is a relatively harder substance than calcium hydroxide. The particles become cemented firmly together. An exhausted granule of soda lime pulverizes with greater difficulty than a fresh one as a result of the change in chemical composition. Exhausted granules are less caustic than unused granules because the alkali is almost entirely neutralized. Some remains in the heart of the granules. A granule of soda lime gains weight as it absorbs carbon dioxide since *in the conversion of the hydroxides to* carbonate one molecule of water, which has a molecular weight of 18, is exchanged for one molecule of carbon dioxide whose weight is 44. The charge of absorbent expands somewhat and becomes tightly packed in a canister after complete exhaustion has occurred.

U.S.P. SPECIFICATIONS FOR SODA LIME

COMPOSITION

Soda lime is included in the United States Pharmacopeia. The Latin name

is *calx sodica.* The U.S.P. requirements for soda lime are broad. The specifications are as follows: The substance should be white and composed of sodium hydroxide, calcium hydroxide, and potassium hydroxide. The U.S.P. recognizes soda lime as a mixture of variable composition and specifies no fixed percentage of alkali. The moisture content of soda lime is variable but should not be less than 14% nor exceed 19% of the weight of the specimen.

ESTIMATION OF MOISTURE CONTENT

The moisture content is determined by desiccation. The U.S.P. recommends that 9½ to 10 grams of the specimen be weighed and dried at 105°C for two hours. The specimen should not lose more than 19% of its weight. Soda lime absorbs moisture. This may be determined according to the U.S.P. technique by placing 9½ to 10 grams of soda lime in a 50 ml. weighing bottle having a diameter of 50 mm. and a height of 30 mm. The bottle and contents are weighed and then placed in a desiccator over sulphuric acid having a specific gravity of 1.6. The bottle remains in the desiccator for 24 hours and is then reweighed. The increase in weight should not be more than 7.5%.

DETERMINATION OF HARDNESS

The hardness is determined by agitating the absorbent with steel ball bearings in a hardness pan. A 50 grams portion of the granules which have been sifted first through a No. 2 standard mesh sieve and then a No. 40 standard mesh sieve are placed in a hardness pan. This is a steel pan which has a diameter of 200 mm. and a concave brass bottom with thickness of 7.9 mm. at the circumference and 3.2 mm. at the center.

The inside spherical radius of curvature is 109 cms. Fifteen steel balls of 7.9 mm. diameter are placed with the specimen and shaken on a mechanical sieve pan shaker for 30 minutes. The steel balls are removed and the contents of the pan are brushed on to a sieve of a 40 mesh size and shaken for three minutes on a mechanical sieve shaker and weighed. The weight of soda lime retained on the screen should not be less than 75% of the weight at the start of the test. This remaining weight in grams is expressed as a number referred to as the *hardness number.* The hardness number should be 75 or more.

DETERMINATION OF ABSORPTIVE CAPACITY

The technique for determining carbon dioxide absorptive capacity outlined by the U.S.P. is as follows: approximately 9½ to 10½ grams of soda lime are placed in a U tube, one end of which is packed with approximately 5 grams of anhydrous calcium chloride. Each end is stoppered with perforated cork. The tube and its contents are weighed. A stream of pure carbon dioxide is first passed through the calcium chloride, then through the absorbent at the rate of 75 ml. per minute for 20 minutes. The tube is again weighed at room temperature. The increase in weight should not be less than 19% of the weight of the soda lime used for the test. This test is an index of the alkali content in the specimen. It is not necessarily an index of its efficacy during clinical use.

PRESERVATION

Soda lime should be packed in airtight containers to prevent changes in moisture content and absorption of car-

bon dioxide from the air. Containers once opened should be tightly covered after desired quantities have been withdrawn.

BARALYME

Mixtures of barium and calcium hydroxide are also used to absorb carbon dioxide. A preparation (Baralyme) was introduced in 1939 by the Thomas Edison Company of New Jersey. The preparation offered for anesthesia consists of a mixture of 20% barium hydroxide and 80% calcium hydroxide. The absorption efficiency of this parallels that of soda lime. The preparation is available in compressed cylindrical tablets $\frac{3}{16}$" in diameter and $\frac{1}{8}$" thick or in a granular form like soda lime. The granular form is a more efficient absorbent than the tablet form. The mass is of sufficient hardness to withstand handling and mechanical abuse in metallic canisters. Silica is not added to harden the particles. The barium hydroxide plays the role of activator in the same manner that sodium hydroxide does in soda lime. Barium carbonate, calcium carbonate and water are the products of the reaction. The heat evolved is quantitatively the same as that resulting from the neutralization of carbonic acid and soda lime. Both barium and calcium carbonates are insoluble and, therefore, do not interact. In soda lime, the sodium carbonate which forms is soluble and interacts with unneutralized calcium hydroxide. Consequently no regeneration of activity occurs in Baralyme as occurs in the case of soda lime when sodium carbonate interacts with the unneutralized calcium hydroxide. Most of the moisture in Baralyme is chemically united with the barium hydroxide in the form of the octahydrate ($Ba(OH)_2 \cdot 8H_2O$). This situation differs from that of soda lime in which the water is present as a film over the surface and in the pores of the granule. The water content of soda lime varies when exposed to dry or humid atmospheres because it is not chemically bound. That of Baralyme does not vary. If Baralyme is heated, however, it does lose its water hydration. Baralyme exposed to a dry atmosphere at 150°C. loses its moisture readily, and as is the case with soda lime, the desiccated material is ineffective in absorbing carbon dioxide. Wetting the dried mixture with water produces a "doughy" mass.

Studies by Kilbourne, Adriani and Batten and others at the time the mixture was first proposed indicated that Baralyme was equally as effective if not superior to soda lime as a carbon dioxide absorbent. The absorbents being compared were those available in 1938. There has been considerable improvement in soda lime since that time. Recent studies by the writer, Elam and others indicate that the improved soda lime presently available (Wilson's Sodasorb, Malinkrodt's) is more effective than Baralyme under identical conditions of exposure to carbon dioxide. The writer effectively absorbed carbon dioxide using a 350 gram charge in an experimental canister for three hours. A charge of soda lime under similar circumstances absorbed effectively for four and a half hours. It is not surprising that the Baralyme is less effective than soda lime since barium is less active chemically than sodium. Barium occupies a lower position in the electromotive series than sodium. Besides, its hydroxide is less soluble than that of sodium. The base, however, is highly ionized and is, therefore, active. Recently potassium hydroxide has been added to the mixture to improve its efficiency.

TOXICITY OF THE BARIUM ION

The barium ion is toxic. Therefore, soluble barium compounds and those which are insoluble but interact with acids and other substances to release the barium ion may be poisonous if taken internally. Barium sulphate may be taken internally because it is insoluble even in the presence of the hydrochloric acid of the stomach. Barium carbonate, on the other hand, would form barium chloride in the stomach. This is soluble and poisonous. It is unlikely, though, that the quantity of dust rising from Baralyme to which a patient is exposed during clinical anesthesia is sufficient to cause any deleterious effects. The mixture has been in use nearly a quarter of a century and no instance of poisoning has been recorded. The toxic nature of barium compounds should be borne in mind when disposing of the exhausted absorbent.

EFFICIENCY OF CARBON DIOXIDE FILTERS

Little was known about the inner workings of the canister in the early days of carbon dioxide absorption. A controlled study under clinical conditions is impossible because many variable factors are involved. Significant data has been obtained in the laboratory using mechanical spirometers which simulate breathing as it is encountered during clinical anesthesia. In this way, the variables encountered clinically are eliminated.

Waters, by repeated clinical trials, noted that absorption was optimal in the to and fro system when he used an 8 × 13 cms. cylindrical canister. The efficiency fell off when he used larger or smaller canisters. The reason became apparent from the laboratory studies of

Adriani and Rovenstine who noted that absorption was optimal when the canister air space and the tidal volume were equal. The bulkiness of soda lime is deceptive. Even though the absorbent appears to fill the entire canister, the volume of air between the granules and within the pores of the granules is surprisingly large. The air space in an 8 × 13 cms. canister packed with 6–8 mesh soda lime varied between 375–425 ml. This air space corresponds closely to that of the tidal volume of an anesthetized patient breathing unassisted. The relationship of tidal volume to air space applies also to the circle filter. Efficiency decreases if tidal volume exceeds air space. However, absorption continues to be efficient if the air space exceeds the tidal volume. More will be said of this later on.

The To and Fro Filter

The statement that efficiency is optimal when air space equals tidal volume requires clarification. It is true only for a variable period of time, after which efficiency gradually decreases as the alkali is neutralized. The question, then, is how long does this efficient absorption last. Studies of the air currents in the canister give some insight to the pattern of absorption. Adriani and Rovenstine visualized the flow of gases by coating granules of soda lime with lead acetate and adding hydrogen sulphide to the gases in the mechanical ventilator. Hydrogen sulphide is an acidic gas. It, therefore, would be absorbed by soda lime in the same manner as carbon dioxide. It also forms lead sulphide which is black. The granules darken as the black lead sulphide forms on the surface. Parallel confirmatory studies were also done in which samples of absorbent

taken from various areas of the canister were analyzed for their carbon dioxide content. Carbon dioxide content is highest in the areas of maximum discoloration. In the to and fro unit the granules at the inlet of the canister darken first. Later those at the outlet darken. The granules at the intermediate section remain unchanged or are grey-tinted. As absorption proceeds, the granules along the sides darken. The granules along the sides darken more than those in the core. The ambient gases follow the path of least resistance. They sweep along the sides of the canister into the bag. Apparently the granules in the core offer more resistance than those along the sides. The granules facing the screens at the mask and bag end darken com-

pletely and soonest. Apparently some carbon dioxide passes with the effluent gases along the sides into the breathing bag, as the gases reverse their direction during inspiration. The surfaces facing the bag are exposed to the inspired gas. These granules remove any unabsorbed carbon dioxide which has passed into the bag. The carbon dioxide concentration in the breathing bag is no index of the amount passing back into the mask. As absorption proceeds and the charge is exhausted the entire surface of the granules at the inlet and in the outlet darkens. The granules in the center are only partly discolored. At terminal exhaustion a rhomboid shaped area composed of partially discolored granules remains at the core of the distal third of the canister
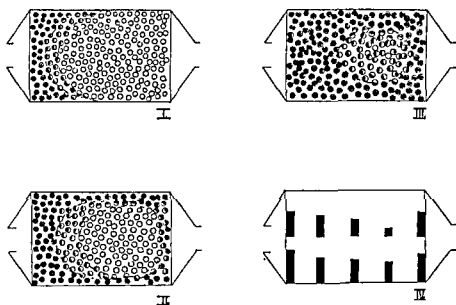
Fig. 4.5. Illustrates the paths the gases follow in the to and fro unit as studied by the darkening of lead acetate by hydrogen sulphide. Solid black granules indicate completely exhausted granules. I shows distribution when charge is first placed in service; II, after prolonged use.—The flow of gases is greater along the periphery. III, after complete exhaustion of the entire charge.—A small "blind spot" remains in the distal (bag end) portion of canister which contains incompletely exhausted absorbent. IV, relative content of carbon dioxide per gram of original alkali in different sections along the center and sides of the canister. (From Adriani and Rovenstine, *Anesthesiology* 2-1-1941.) (Courtesy of *Anesthesiology.*)
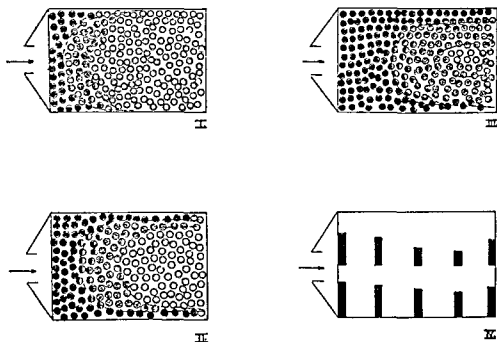
FIG. 5.5. Air currents in circle type absorber. Drawn in same way as Fig. 4.5. The pattern ultimately is similar to that in the to and fro filter. (From Adriani and Rovenstine, *Anesthesiology*, 2-1-1941.) (Courtesy of *Anesthesiology*.)

(Fig. 4.5). The granules on the periphery of this area are discolored on the surface facing the sides and white on the surface facing the core (Fig. 5.5).

The absorbent analyzed from this "blind spot" contain less carbon dioxide per gram of original alkali than that removed from the sides or front. In the order of highest concentrations of carbon dioxide are (1) the granules along the sides, (2) the granules at the mask end, (3) those at the core, (4) those at the inlet, (5) those at the side of the canister at the bag end and (6) those at the core at the bag end (Fig. 4.5).

EFFICIENCY OF THE TO AND FRO FILTER

An 8×11 cm. cylindrical canister, often referred to as a standard Waters canister, filled with 4–8 mesh soda lime (Sodasorb) tested on a mechanical ventilator using a tidal exchange of 500 ml. 20 times per minute with a flow of 200 ml. carbon dioxide per minute absorbs for 5–6 hours before terminal exhaustion occurs. A progressive increase in the return of carbon dioxide up to a 0.5% average return occurs within 5½ hours. During the first 1½ hours the gases returning to the mask contain less than .05% carbon dioxide. The concentration gradually increases until the point of terminal exhaustion. The concentration in the effluent gases at the mask end depends upon the moment of sampling. It is maximal, as one would expect, at the beginning of inspiration because the gases containing unabsorbed carbon dioxide in the dead space are the first to be drawn into the mask. It is least at the end of inspiration. The overall mean concentration during inspiration increases with canister use. This, as will be explained later, is due to a progressive extension of the dead space inward as the canister is used.

The same period of absorption is obtained as the size of the canister is decreased, provided the tidal exchange and carbon dioxide input is decreased in

proportion to the air space. The period of effective absorption is shortened as the carbon dioxide input is increased.

The Circle Filter

The circle filter was studied utilizing the same techniques. The pattern of absorption in the circle filter differs somewhat from that of the to and fro. The gases pass into the circle filter, as has been mentioned previously, in a different manner and apparently with less force than in the to and fro filter. Much of the force of the exhaled gas is expended as friction in the tubes and through the valves in the circle system. In the to and fro filter, the force of the respired gases is expended directly against the granules of absorbent. Colored granules placed at various sites in a tightly packed canister, in the course of four or five hours, migrate several centimeters in to the to and fro. In the circle filter such migration of granules is slight. Lead impregnated granules exposed to hydrogen sulphide at first undergo a spotted discoloration instead of becoming uniformly darkened as they do in the to and fro. Discoloration is absent at the points of contact of contiguous granules. As is the case of the to and fro, the gases sweep along the sides preferentially. Ultimately the granules are uniformly darkened in a similar manner to that of the to and fro. A rhomboid shaped area or "blind spot," similar to that found in the to and fro, is also present in the terminal third of the canister. Chemical analyses of samples of the absorbent removed from various parts of the canister reveal the pattern of exhaustion to be similar to that of the to and fro. The greatest concentration of carbon dioxide is in the granules at the inlet and along the sides (Fig. 5.5). The concentration

decreases progressively towards the outlet. In large canisters the absorbent at the outlet half of the canister is less than 50% exhausted at the time carbon dioxide appears in detectable amounts at the outlet. Methods of utilizing this absorbent to its fullest capacity are described further on.

Mention has been made that in the circle filter absorption is efficient as long as the tidal volume is equivalent to or less than the air space in the canister. When the tidal volume exceeds the air space of the canister, efficiency, as in the to and fro filter, likewise falls off. The gases do not come to rest and remain in contact with the absorbent, since they are not entirely accommodated by the air space. When the tidal volume is equal to or smaller than the air space the gases advance through the canister in a pulsating fashion during each expiration. The effluent gases pass into the breathing bag from which they are drawn during inspiration. Except for movement due to efflux, influx and to diffusion, the gases in the canister are stationary in the air space during the expiratory phase of respiration. It is advantageous in the circle filter, therefore, to have a canister which has an air space larger than the tidal volume because this periodic advance permits longer contact with the absorbent. The larger the canister the longer the period of uninterrupted use. The average concentration of carbon dioxide in the effluent gases is uniform. The moment to moment variations are not significant.

AIR SPACE

The importance of the air space in a canister has been alluded to and emphasized in the preceding paragraph. The total air space is composed of the space

between the granules, or intergranular space, and that within the granules or intragranular. Absorbents have varying degrees of porosity. The total air space in a given quantity of absorbent may be *computed by the method of specific gravity* or by actually displacing the air with water, cyclohexane or other fluids. The intergranular air space varies with the number of granules in a given volume. The smaller the mesh of soda lime the greater the number of granules and the total weight of absorbent and the less the air space. The pore air space varies with the moisture content. The low moisture limes have more than the high moisture, since the water occupies the pores. It is doubtful that a true measure of the air in the pores can ever be obtained. As absorption proceeds the pore space decreases. The total air space is anywhere from 40–60% of the total volume of a canister depending upon the particular absorbent examined (Fig. 6.5). The pore air space is .2 to .3 ml. per gram and is approximately the same for either Baralyme or soda lime.

TIME EFFICIENCY

The effectiveness of the absorbent in completely removing carbon dioxide is sometimes referred to as the *absorption efficiency*. An absorbent may be highly active and completely remove carbon dioxide for a short interval of time. The time the absorption acts is called *time efficiency*. Sodium hydroxide sticks, for example, are highly efficient in absorbing carbon dioxide. However, they soon become coated with sodium carbonate, after which effective absorption ceases because the gas does not penetrate the carbonate film. Such an absorbent is said to have a high absorption efficiency but a poor time efficiency because it absorbs
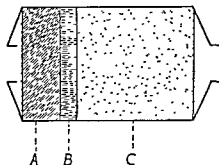
Fig. 6.5. The space actually occupied by the absorbent (A), the intragranular air space (B) and the intergranular air space (C) of an 8 × 13 cm. cylindrical canister charged with 4 to 8 mesh soda lime.

well while it absorbs but it absorbs for only a short time. All the available alkali is not utilized. The ideal absorbent possesses both types of efficiency. Both the absorption and time efficiency of soda lime are high.

COMPLETENESS OF ABSORPTION

Adriani and Rovenstine and later Conroy and Seevers showed that at no time is there absolute, complete removal of carbon dioxide in a canister using soda lime. A trace passes through at all times. This trace at first is not detectable by the ordinary methods of analysis. The carbon dioxide concentration is far less than is found in the atmosphere and, therefore, of little consequence. That carbon dioxide comes through in traces is not difficult to understand when one considers the process of absorption. The distance between granules compared to the size of a molecule of carbon dioxide is relatively great. It is conceivable that some molecules of carbon dioxide slip through without ever coming into contact with the soda lime granules. Then also, carbon dioxide is not highly soluble. Many of the molecules which do come into contact are not dissolved in the moisture in the soda lime granules

and are, therefore, not neutralized. They too pass on through. Carbon dioxide is poorly ionized and forms a weak acid. Therefore, it is not immediately neutralized and this retards its absorption. Gradually, as the alkali on the surface of the granules in various parts of the granule is neutralized, more carbon dioxide molecules, since they are not neutralized, pass through. The effluent concentration increases and soon reaches a detectable level. The concentration at this point may still be less than is ordinarily found in the atmosphere and of no clinical significance. The concentration continues to increase and finally reaches a point at which it is no longer tolerable to most patients. Shortly afterward terminal exhaustion occurs.

The concentration of carbon dioxide which can be recirculated in this manner differs immensely from patient to patient. Generally, in most patients, when concentrations of 0.5% are returned to the mask the effects of hypercapnia become noticeable. Many anesthetists still feel that a little carbon dioxide does no harm. One must remember that the absorption technique was introduced at a time when the semi-closed technique with rebreathing was universally employed. Some degree of hypercapnia was considered desirable at that time. The contrast between the hyperventilation using the semi-closed system in vogue when absorption was introduced and the quiet breathing during the absorption technique was so striking that the imperfections of closed system anesthesia were not appreciated for some time. Gradually it was realized that some patients tolerated incomplete removal of carbon dioxide better than others. This has led to reappraisal of carbon dioxide filters. As a result three schools of thought exist at the present time: (1) the school that says total removal should be achieved but cannot be achieved, (2) the one that feels that "a little carbon dioxide does no harm" and continues to use the to and fro filter and filters of older design and (3) the school which states that carbon dioxide must be and can be completely removed by absorption with alkali. Extensive experiments by the writer and his associates, Brown, Elam and others indicate that complete removal is possible if one desires it. This is achieved by using the circle filter with a large canister or one with canisters in series. This is described further on in this chapter.

VARIABLE FACTORS IN ABSORPTION

DURATION OF INSPIRATION

The duration of inspiration and expiration appears to have no effect on the efficiency of absorption in the circle filter. In laboratory studies using a mechanical ventilator no difference was found in absorption when inspiration equalled expiration, when expiration was ⅓ of the cycle and inspiration ⅔ and inspiration ⅓ and expiration ⅔.

EFFECT OF HUMIDIFICATION

Since water plays an important role in the reaction of neutralization one would assume that absorption is more effective when the gases are humidified. However, this is not the case. Absorption is as effective when the gases are unhumidified as when humidified as long as soda lime of a high moisture content is used. The moisture obviously must be incorporated within the granule to be of benefit. Thirty minutes after a canister is in use in either the to and fro or the circle

system, the moisture from the reaction of neutralization raises the humidity to nearly 100%. Still, if a low moisture absorbent is used in the presence of 100% humidity absorption is not satisfactory.

POSITION OF CANISTER

The position of the canister, likewise, is immaterial provided the canisters are tightly packed with absorbent so that channeling does not occur. Absorption is as effective when the canister is placed horizontally as when it is placed vertically. Absorption is equally as effective when the gases pass through the soda lime from below upward through a vertically placed canister as from above downward.

SHAPE OF CANISTER

Globular, oval, conical, oblong, and other shaped canisters may be used to absorb carbon dioxide with approximately the same efficiency, provided the tidal volume of the gases is equal to the air space in the canister. Differences of clinical importance may be due to resistance to the passage of gases rather than to absorption or time efficiency (Fig. 5.7).

MATERIAL FOR CANISTERS

Canisters may be constructed of metal, usually brass or steel. Recently, plastic canisters have become popular because of transparency. Metals possess an advantage over plastics because they withstand contact with heat and alkalis. Besides they conduct heat better than most plastics. This helps dissipate heat resulting from the chemical reaction. This is especially important in the to and fro unit. The early plastic containers were not satisfactory because etching occurred from the effects of the alkali or they tended to warp from the effects of heat. This in turn caused leaks in the

system. Frequently they became stained by the indicator dye and became useless for detecting color changes. There have, however, been improvements in plastics so that present day containers are more satisfactory.

CHANNELING

A phenomenon referred to as channeling may cause considerable reduction in efficiency which leads to hypercarbia and a waste of soda lime. Unless the absorbent is packed tightly and uniformly the gases follow the path of least resistance and create channels directly from the inlet to the outlet of the canister. They, thus, bypass the bulk of the granules of absorbent and incomplete neutralization occurs. These channels may be visualized by using hydrogen sulphide on the lead acetate coated granules mentioned heretofore. Streaks of partially darkened granules radiate throughout the mass of absorbent when channeling occurs. The sides of the canister should be tapped as it is filled to assure uniform filling. A clamp type of screen on top to tightly fix the mass assures no movement of the granules (Fig. 8.5). Channeling may also be caused by faulty canister design. Channeling is prone to occur in canisters having bypass tubes in the center. Disks referred to as baffles are sometimes placed at the inlet or outlet to divert the gases in a more uniform fashion throughout the canister. A channel is often established in a to and fro filter along the top of the canister particularly when it is held horizontally or is partly inclined. The constant handling of the canister causes fragmentation of the granules, especially when it is not tightly packed. The sifting together leaves a void which results in a channel from inlet to outlet.
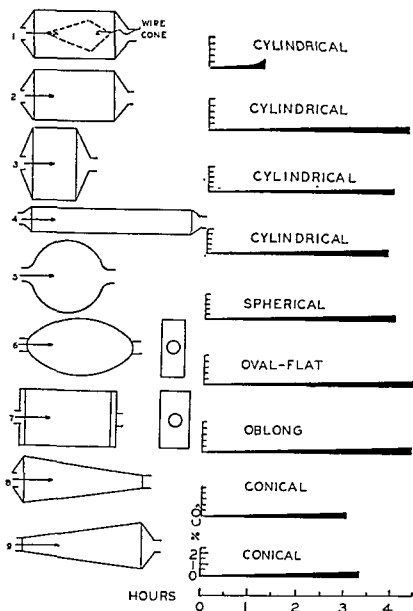
FIG. 7.5. The effect of variations in the shape of the canister upon the efficiency of absorption of carbon dioxide by soda lime. The volume and inter and intra-granular air space, tidal volume and respiratory rate are the same in each trial. (From Adriani and Byrd, *Anesthesiology*, 2:450, 1941. Courtesy of *Anesthesiology*)

REGENERATION OF ACTIVITY— "PEAKING"

Early in the use of carbon dioxide absorption a phenomenon referred to as "peaking" was reported. This was more obvious in the circle than in the to and fro filter. Adriani and Rovenstine found, after aerating 8×13 cm. canisters charged with soda lime using a tidal volume of 500 ml., a respiratory rate of 20 and a carbon dioxide output of 200 ml. per minute, that absorption rapidly fell
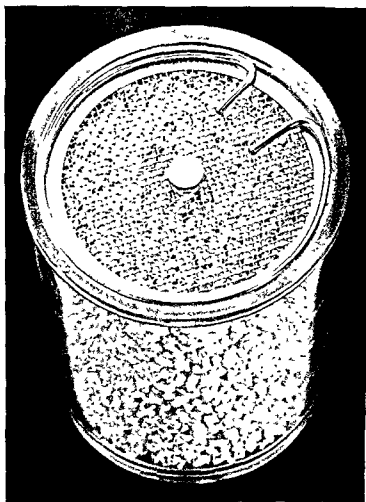
Fig. 8.5. Clamp-type screen to assure tight packing of
canister with absorbent to avoid channeling

off after 5 hours in the to and fro filter (Fig. 9.5) and after 2½ hours in the circle filter (Fig. 10.5). They further observed that the soda lime was not completely exhausted and that these end points were only apparent. When the charge was set aside and allowed to remain idle for a period of several hours and aerated again under the same conditions, absorption proceeded nearly as efficiently as before but for a shorter period of time. This was true in both types of units.

After a number of such intervals of efficient absorption with intervening "rest" periods, terminal exhaustion occurred since the bulk of the hydroxides were all converted to carbonates. Each

interval of efficient absorption was shorter than the preceding one, totalling six to seven hours before a 500 gm. charge was completely exhausted. In the to and fro filter a second period lasted approximately one hour, the third one-fourth to one-half hour. Gram for gram, approximately the same total time efficiency was obtained per 500 gm. of absorbent in each type of unit when comparisons were made under identical conditions. More frequent "rest" periods were essential in the circle filter than in the to and fro.

This reactivation is explained by the fact that *sodium hydroxide*, *which is more soluble and more active chemically*

than calcium hydroxide, combines preferentially with carbon dioxide to form sodium carbonate. Sodium carbonate, because it is soluble, dissolves in the moisture in the granule. It, thus, can permeate into the granule and react with the less active and less soluble unneutralized calcium hydroxide to form calcium carbonate and sodium hydroxide. The moisture in a soda lime granule forms a film on the surface within the porous mass of calcium hydroxide composing the granule. This moisture is actually a solution of both hydroxides. Since sodium hydroxide is more soluble

than calcium hydroxide it predominates in the water film. Upon exhaustion the film contains predominantly sodium carbonate. The following equation indicates the reactions which occur:

$$2NaOH + H_2CO_3 \rightarrow Na_2CO_3 + 2H_2O$$
$$+$$
$$Ca(OH)_2$$
$$+$$
$$2NaOH + CaCO_3$$
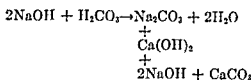
This reaction is not reversible since calcium carbonate is insoluble. The regenerated sodium hydroxide imparts renewed activity to the absorbent. Sodium hydroxide is soluble in alcohol while the
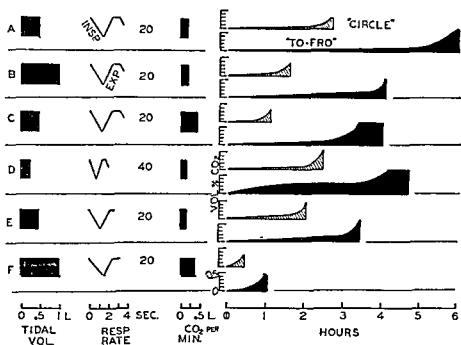
Fig. 9.5. A comparison of the time interval during which efficient absorption occurs in the to and fro and circle type of unit used for carbon dioxide absorption and the effect of variations in tidal volume, respiratory rate and carbon dioxide output per minute. (A) Absorption with normal tidal volume and respiratory rate. (B) Effect of increasing tidal volume, maintaining respiratory rate and CO₂. (D) Increased respiratory rate with normal minute volume exchange obtained by decreasing tidal volume. (E) Effect of increased respiratory rate (F) Increase of both tidal volume and output of CO₂. These comparisons were made on canisters of the same size and under the same experimental conditions. The curves represent the concentration of unabsorbed carbon dioxide which passes through the filter. (From Adriani and Byrd, *Anesthesiology*, 2-450-1941.) (Courtesy of *Anesthesiology*.)
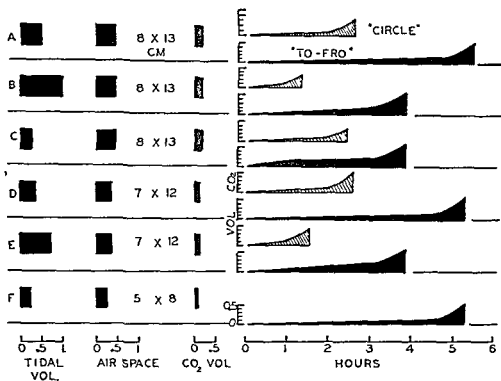
Fig. 10.5. The relationship of tidal volume of the patient to the total air space within a canister charged with absorbent. The optimum absorption efficiency is obtained when the tidal volume equals the air space within the canister as shown in A, D and F. Comparisons were made on 8 × 13 cms cylindrical canisters charged with 4–8 mesh soda lime. (From Adriani and Byrd, *Anesthesiology*, 2-450-1941.) (Courtesy of *Anesthesiology*)

other ingredients in soda lime are not. Foregger, utilizing this fact, showed that sodium hydroxide regenerates when exhausted soda lime "rests." Calcium hydroxide also *absorbs carbon dioxide directly* to form calcium carbonate without this intermediary reaction, but this direct reaction is less prominent. One can see how calcium hydroxide is the mainstay of the absorption process and ultimately performs the bulk of the task of absorption. The sodium hydroxide, however, is necessary to maintain the necessary activity.

DUAL CANISTERS

The older filters were equipped with dual canisters with a selector valve to permit alternation of charges. One charge could be bypassed while the other "rested." During this period of idling its charge became reactivated while the other was in operation. In recent years soda lime has been improved so that this "peaking" is seldom seen in present day practice (Fig. 11.5). Thus, *alternation of canisters no longer appears* to be necessary. The interaction between the soluble carbonates and calcium hydroxide still occurs but keeps pace with absorption. The elimination of the lag heretofore observed may be ascribed to the following improvements in soda lime. These are: (1) Less silica is now used. This reduces the hardness which facilitates the permeation of the soluble constituents into the granules so that the interaction of carbonates and hydroxides can occur. (2) The moisture content is better controlled and more uniform and
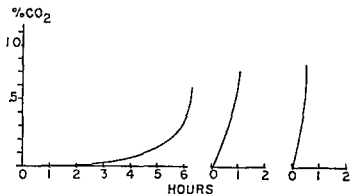
%CO$_2$

HOURS

higher. Moisture is necessary for the interaction to occur and maintain the pace with absorption. (3) Small quantities of potassium hydroxide (1%) are now added to soda lime. This enhances the activity of the absorbent.

TEMPERATURE DURING ABSORPTION

Sources of Heat

The reaction of neutralization is exothermic. Consequently canisters warm up when in use. The heat which is evolved, however, is not all derived from the reaction of neutralization. Another source is the heat of solution. The amount evolved from this source is negligible when using present day absorbents because the sodium hydroxide content is low and moisture content is high. Solution of the hydroxide has already occurred. Absorbents which contain high percentages of sodium hydroxide and low moisture release heat as they absorb water due to the hygroscopic properties of sodium hydroxide. Heat is also evolved when the moisture condenses in the breathing bag and tubings. This moisture has a dual origin—from the patient's lungs and from the condensation

of the water vapor liberated by the reaction of neutralization. Some heat is also added from the exhaled air. The bulk of the heat is due to neutralization, however.

Temperature in the Canister

The temperature of the reacting absorbent in the heart of a to and fro canister, at times, may exceed 60°C. This, since the canister is so close to the face piece, frequently causes the inspired air to be warmed above body temperature (39° ± 42°C.) (Fig. 12.5). When a freshly charged canister is placed in use the temperature in the front third ranges between 55° and 60°C., that in the center portion ranges between 50° and 55°C. and that in the distal third portion averages 40° to 45°C. As absorption proceeds, the temperature in the center rises to 60°C., at the end to 50°C., while the front end falls to approximately 50°C. These temperatures were observed when tips of the thermometers were placed in the soda lime approximately 2 cms. below the edge of the canister. As a charge in a canister becomes exhausted, that in the front falls to 40°C., that in the center to 50°C., and that in the end rises to 60°C. Temperatures in all portions of

Fig. 12.5. Comparison under identical ventilating conditions of temperatures in mask using circle filter (Foregger with 30" × 1¼" corrugated tubing) and to and fro (13 × 8 cm. brass canister). The time in minutes required to reach a steady state is also shown.
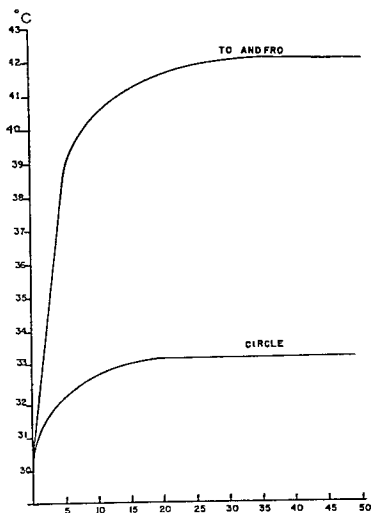
the canister drop as soon as terminal exhaustion occurs. A cool canister usually indicates the absence of chemical activity and inadequate absorption. However, a low carbon dioxide output may not liberate sufficient heat to warm the canister.

A pattern of temperature ranges similar to the to and fro is also noted in the circle filter. The average range, however, is approximately 5°C. less than in the to and fro. This is understandable since the opportunity for loss of heat by conduction, convection and radiation is greater in the circle filter. The temperature of the jacket of a circle filter offers little clue to that in the interior of the reacting absorbent. Palpation of the canister yields more information in the case of the to and fro than the circle filter.

Temperature in Mask

Since the inspired gases may be above body temperature in the to and fro unit heat is not only retained by the patient but it may even be added to his respired gases. Heat retention, therefore, is a possibility using the to and fro. In the circle filter the tubing is long and the soda lime chamber is large. The tubes, valves and canister help dissipate the heat. The temperature in the face piece in the circle system varies with the type of unit but rarely exceeds 32°–33°C. (Fig. 12.5). The heat output and the resultant temperatures, of course, vary with the carbon dioxide output of the patient, the environmental temperature, the length of the tubes, the size of the canister and the area from which radia-

tion occurs. Carbon dioxide output is increased in fever, thyroid disease, and other conditions in which metabolic rate is elevated. In these instances temperatures in the inhaler may be higher and time efficiency of the absorbent shorter, since the reacting quantities are greater. The temperature of the outside of a chrome plated steel canister in the to and fro unit averages twenty degrees less than that of the mass inside under ordinary conditions of usage. The degree of warmth of the exterior of the canister is not a reliable index of the efficiency of absorption. The canister may feel cool, even though absorption is efficient if carbon dioxide output is low. On the other hand, a hot exterior may result if carbon dioxide output is high even though the gas is not completely removed.

TEMPERATURE OF GASES ENTERING THE CANISTER

The temperature of the gases entering the canister does not appreciably influence the absorption efficiency from a clinical standpoint. Canisters ventilated with air containing 2% carbon dioxide at 0°C., 28°C. and 100°C. effectively filtered carbon dioxide in each case. The velocity of a chemical reaction increases as the temperature rises. However, any differences in velocity of the chemical reaction are of no apparent practical importance.

ABSORBENTS CONTAINING INDICATORS

Soda lime is impregnated with dyes which change color when the hydroxides are neutralized and converted to carbonates. Many compounds have different colors at different hydrogen ion concentrations. These color changes occur because these compounds are acids or bases

which enter into proton transfer reactions converting a base into an acid or vice versa. The acid form has a different color than the base form. Methyl orange, for example, is a weak organic base which is orange in color. When converted to an acid it turns yellow. Between pH 6.8 and 8.4 the base and acid are both present in varying proportions, so that the color varies from shades of yellow to orange. These various shades of color may be used to determine the hydrogen ion concentration of a solution. Some indicators are acids which form salts with bases. Phenolphthalein is an example of a weak, colorless organic acid which is converted by a base to a pink soluble substance. Ethyl violet is a colorless base which is impregnated in soda lime. The base reacts with carbonic acid to form the soluble carbonate which is purple. When all the sodium hydroxide is converted to sodium and calcium carbonate, a purple color develops. Clayton yellow is also used as an indicator for soda lime. The basic form is red, the acid form yellow. Soda lime granules impregnated with the dye appear pink; when exhausted they are yellow. The color change occurs at a high pH range.

Soda lime with indicators was first received with enthusiasm when the idea was first conceived. However, after extensive clinical trials, it was found that the physiologic end point, that is, the point at which hypercarbia becomes intolerable, did not coincide with the chemical end point (the point at which the color change occurred). Usually, signs of hypercarbia appear before the color change. In some filters, after a charge of absorbent has been in use some time, the granules along the side of the canister change color, while those in the center have not changed color, since

the gases sweep along the side more easily than through the center. Thus, a color change along the sides is not necessarily an index of the state of the absorbent throughout the entire canister. Carbon dioxide may be leaking through due to channeling without any color change of the granules facing the canister. Also a color change may occur and disappear after the change stands. This reversal of the color change is due to regeneration and reformation of traces of sodium hydroxide. This change may occur when the absorbent is exhausted sufficiently to be of no further value clinically, but still contains enough alkali to cause sufficient regeneration to effect these color changes. Thus, up to now indicators have been of little service. However, indicators are of value in the circle system if two canisters are placed in series. The absorbent is used until a color change occurs in the first canister. This canister is removed and replaced by the second one and a fresh charge is placed in the position occupied by the second canister. This "in series" arrangement is described further on. It must be emphasized that the only final assurance of complete removal is to use a method of detecting carbon dioxide at the outlet of the filter.

COMPLETENESS OF UTILIZATION OF ALKALI

Utilization of a charge of soda lime to the point of complete neutralization of its contained alkali does not occur. The percentage utilized varies widely under different clinical conditions, with the type of absorbent and with the type of canister. Even under ideal circumstances, 100% utilization of the alkali does not occur. Some alkali in the heart of the granule remains unused at the point of

terminal absorption when intolerable quantities of carbon dioxide are returned. One gram molecular weight of calcium hydroxide (74 gm.) theoretically absorbs 22.4 liters, or 44 grams of carbon dioxide provided the conversion is to calcium carbonate alone and no bicarbonate forms. Conversion of the carbonate to bicarbonate would increase the quantity of carbon dioxide absorbed. The formation of bicarbonate, as has been mentioned previously, is of no clinical consequence since intolerable quantities of carbon dioxide would filter through by the time this reaction was occurring to any appreciable extent. A gram molecular weight of sodium hydroxide (40 gm.) absorbs 22 grams, or 11.2 liters of carbon dioxide. The theoretical capacity of soda lime for carbon dioxide cannot be stated since soda lime is a mixture of two hydroxides and water. The capacity varies with the composition. During actual use the ease with which the gas penetrates into and neutralizes the alkali in the heart of the granule is important. This depends on porosity and hardness. The porosity varies from specimen to specimen. It varies as absorption proceeds because the pores may fill with water or dust or they may be occluded by the expanding carbonates.

The carbon dioxide content of the granules varies in different parts of the canister. It is greatest in the granules at the inlet and along the sides of the canister. The utilization of the theoretical capacity of soda lime may be as low as 35% in one part of the canister of a circle system and as high as 85% in another. The average of all granules is approximately 50% in canisters used singly and 70% in those used in series. Some granules are found to be neutralized to a lesser extent than others when the

charge as a whole is no longer clinically effective.

DIVIDED CANISTERS AND CANISTERS IN SERIES

Complete removal of carbon dioxide from the effluent gases is possible using a circle filter but not a to and fro. Some carbon dioxide returns to the mask; except for a period of approximately one hour, when a charge is first placed in use in the to and fro. It has been mentioned that minute traces of carbon dioxide which are not detectable by ordinary methods pass through a circle filter from the moment a fresh charge is placed in use. This slight trickle increases gradually and finally a point is reached where it becomes detectable. If the absorbent is discarded as soon as carbon dioxide

Fig. 13 5. The alkali in the absorbent may be utilized to its fullest extent in the circle filter by dividing the canister into two sections. Absorbent in upper section (1) is terminally exhausted as evidenced by change in color of indicator while that in lower half (2) is partly exhausted. (A) Absorbent is utilized to its fullest extent by shifting lower section 2 to upper position and recharging section 1 and placing in lower position (B). Absorbent in section 2 changes color when terminally exhausted, but that in 1 is only partly used (C). Section 2 is replaced by 1 and 2 is recharged (D). The process is carried on ad infinitum.

first becomes detectable, a certain amount of soda lime is wasted. The granules at the inlet half of the canister are almost completely exhausted so that they no longer absorb carbon dioxide. The granules at the exit half are partially exhausted and are still capable of neutralizing carbonic acid, although not as effectively as when fresh. In order to utilize this partially exhausted absorbent to its fullest extent, Brown and Elam have suggested using an exceptionally large transparent canister holding 2200 grams or more. This is divided into two sections of equal size, each of which can be interchanged (Figs. 13.5, 14.5). The absorbent at the inlet section is used until the indicator changes color completely throughout the entire section. The absorbent at the outlet half is still active. Therefore, no carbon dioxide passes from the canister at this point of color change. The exhausted section is removed and replaced by the lower, partly exhausted section. The exhausted *absorbent in the upper section is replaced by a fresh charge. The freshly charged section is placed at the outlet (lower) half. The process is repeated ad infinitum. This arrangement is actually two canisters in series. Each compartment *should be of sufficient size to accommodate the maximum anticipated tidal exchange in the air space of the canister.

The writer has modified the double canister filter so that both canisters may be used in series at one time or each may be alternated singly, whichever way one desires (Figs. 15 5, 16.5). The gases pass through the first canister into the breathing bag on expiration. On inspiration they are drawn from the bag through the second canister. The first canister is used until the indicator
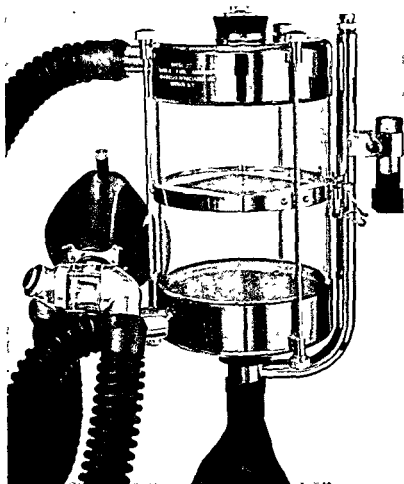
Fig. 14.5. The Roswell Park circle filter employs divided canisters.

changes color, after which it is replaced by the second which is inverted and used until it also changes color. The exhausted absorbent in the first canister is discarded and the replenished canister is placed in the second position. A 450 gram charge lasts six hours, and absorbs 200 ml. carbon dioxide per minute. The carbon dioxide content of the gases in the breathing bag is 0.5% at this point. That of the effluent gases in the second canister is zero. The process is repeated ad infinitum.

CARBON DIOXIDE DETECTORS IN THE EFFLUENT STREAM

One is never certain that absorption is complete and that the filtered gases are carbon dioxide free unless a detector is placed at the outlet of the canister. Channeling, failure of the indicator, the use of absorbent of low alkali or moisture content, or low degree of porosity or exceptional hardness and leakage at the valves are some of the factors responsible for unrecognized incomplete removal. No simple reliable detector is available. Devices for detecting and quantitatively determining the concentration of carbon dioxide in the effluent gases have been introduced from time to time, but thus far none has proved practical. These devices employ either physical or chemical methods of detection. In the chemical detectors the volume of gas necessary to neutralize a given volume of a dilute
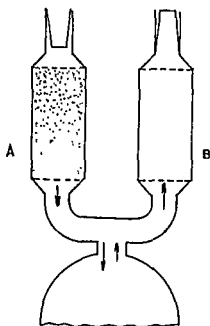
FIG. 15.5. Circle system with canisters in series. The charge in canister 1 (left) in position A is used until indicator dye changes color throughout the charge. At this point charge in canister 2 (right) is only partly exhausted. Canister 2 is placed in position A and canister 1 is replenished and placed in position B and used until indicator changes color. Partly used 1 is returned to position A and refilled 2 to position B. Gases are filtered on inspiration and expiration.

traces of carbon dioxide which unavoidably leak through are, in due time, absorbed in sufficient quantity to convert the dye to the basic form. This occurs although the concentration of carbon dioxide following through has not changed. The Liston-Becker (Chap. 7) infra-red analyzer may be used. This is extremely
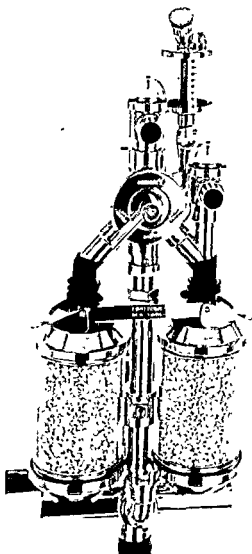
FIG. 16.5. Adriani filter using canisters in series. Traces of unabsorbed CO_2 passing into breathing bag on expiration are absorbed during inspiration by second canister. See legend Figure 14.5.

solution of calcium or barium hydroxide containing an indicator is determined. The gas is drawn from the filter with a calibrated bulb and forced in the form of fine bubbles through the alkali. The percentage of carbon dioxide present is determined by the number of squeezes or bulbsful necessary to effect a color change. One difficulty which has been encountered is that the alkaline dust coats the tubing and finds its way into the solution in the detector and renders the method of questionable value. The placement of strips of impregnated paper with indicators at the exit of the canister has been recommended. These are not satisfactory because the minute

sensitive, but is cumbersome and impractical for ordinary use in an operating room.

DUST FORMATION

Fragmentation of particles of absorbent causes alkaline dusts to pass into the system. This is irritating to the upper respiratory passages. Dust formation is a greater problem in the to and fro unit than in the circle. Dust formation is obviated by increasing the hardness of the absorbent by adding silicates and other cementing substances. Increasing the hardness decreases the absorption efficiency. In the circle filter the canister is away from the face piece and in a fixed position. Not only is fragmentation minimized, but whatever dust forms is deposited in the tubing, bag and the valves. Wetting the interior of the breathing tubes helps to gather the dust. Soft grades of soda lime are troublesome. Air must be blown through the canister frequently to remove the dust before use.

RESISTANCE CAUSED BY SODA LIME

Soda lime contributes to the resistance an inhaler offers to pulmonary ventilation. This resistance, however, is only a fraction of the total ordinarily found. Most of it is introduced by the respiratory valves and tubes which cause turbulent flow and friction. Any impedance to the flow of gases causes fluctuations in mask pressure. A negative pressure develops during inspiration. This returns to zero at the end of inspiration, after which a positive pressure develops during expiration. The pressure then returns to zero at the expiratory pause (Chap. 3). Increases in resistance raise these pressures in either the negative or positive phases or both, depending upon the type

and location of the impedance. The resistance is expressed in terms of pressure in millimeters of water.

Resistance from soda lime is least when coarse mesh granules are used. The number of granules of absorbent per cubic centimeter of space is, relatively speaking, small. The surface exposed to the gases per gram of soda lime is, therefore, correspondingly low. An average of eight granules of a 4 mesh soda lime may occupy one cubic centimeter of space. Friction and turbulence, therefore, are not as great using this size absorbent. However, absorption efficiency is poor. On the other hand a fine mesh absorbent, as for example a 20 mesh, presents a correspondingly larger surface since more granules are found per unit volume. Sixty-four granules of a 20 mesh soda lime fit into one cubic centimeter. Absorption efficiency is higher but there is more turbulence. The impedance offered to the moving gas is greatly increased due to the added number of particles. The optimum absorption efficiency with a minimum resistance is obtained when a blend of 4–8 mesh (approximately 20–30 granules) is used for inhalation anesthesia. A thousand grams of absorbent introduces a resistance of $\frac{1}{2}$–1 mm. H_2O when ventilation is occurring using a 500 ml. tidal volume 20 times per minute with inspiration equalling expiration in a cylindrical canister 8 cms. in diameter.

SHAPE OF CANISTER AND RESISTANCE

The shape of the canister influences both resistance and efficiency of absorption. Oblong, cylindrical, spherical and oval shaped containers introduce the least resistance and are the most satisfactory from this standpoint. Conical
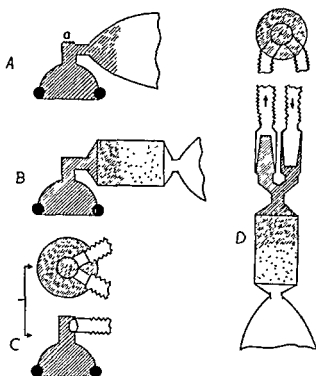
FIG. 17.5. The dead space or space containing air which may be rebreathed without being freed of carbon dioxide in various types of appliances for inhalation anesthesia is represented by shaded areas. (A) The semi-closed system which consists of a mask, equipped with exhalation valve and breathing bag. (B) The to and fro unit. The front part of the canister acts as dead space if the absorbent becomes exhausted if a canister of proper size is not used. (C) The circle filter. The dead space in this unit is confined wholly to the mask if the valves function properly. (D) A unit embodying both the features of the to and fro and circle systems. The valve cages add to the total dead space.

shaped, narrow cylindrical shaped and rectangular canisters offer greater resistance to passage of respiratory gases than wide cylindrical shaped. The rectangular canisters are less efficient because the absorbent in the corners is not utilized.

DEAD SPACE IN REBREATHING UNITS

Mechanical dead space is an important aspect of the rebreathing technique. Dead space has been discussed in a general way in Chapter 3. Mechanical dead space is the space occupied by gases which do not come into direct contact with the absorbent. It represents the space occupied by gases inhaled without being freed of carbon dioxide or replenished with oxygen. The mechanical dead space in the circle filter is that volume of air in the mask and connecting pieces up to the outlet tube (Fig. 17.5). Incompetent valves in a circle filter cause rebreathing and, therefore, increase dead space. Collapse of the corrugated tubes during inspiration, likewise, causes rebreathing and increases dead space. Back diffusion and back recoil of the column of gases into the tube also contribute to the total dead space. These factors are eliminated when properly seating valves are placed on the mask and the tubes are pliable but not collapsible. In the to and fro mechanical dead space is the volume of gases in the mask up to the screen of the canister. The dead space increases progressively from the screen inward in the to and fro, especially if tidal volumes are less than the air space in the charged canister. The face piece accounts for much of the dead space of closed inhalers of either type. The dead space in large masks or face pieces may be as much as 200 ml. The dead space in the mask of infants and children is proportionately greater in relationship to tidal exchange than it is in adults. Tubings or connecting pieces without valves interposed between the canister and mask further increase mechanical dead space.

Both the mechanical and physiological dead spaces are reduced to a minimum during intratracheal anesthesia, since the catheter eliminates the dead space in the naso- and oropharynx and the mask. The anatomical dead space offsets rapid and abrupt changes in al-

veolar carbon dioxide and oxygen tensions. Increases in mechanical dead space ultimately cause increases in alveolar carbon dioxide tension. This may be intolerable to individuals susceptible to slight changes in carbon dioxide tension and causes them to develop respiratory and circulatory disturbances. Dead space is a vexsome problem when using closed systems for anesthesia for infants and children. Even the smallest mask may increase the total dead space beyond the tolerable limit in children and young adults because the tidal volume is so low and the pharynx and trachea are small. In pediatric anesthesia the space in the mask and connecting pieces is, at times, out of proportion to the tidal volume. The open techniques of anesthesia have been employed for many years for pediatric surgery because hypercapnia was uncontrollable due to inadequacy of available apparatus for infants and children.

DEFICIENCIES OF TO AND FRO SYSTEM

The dead space in the to and fro canister extends progressively inward from the screen in the front part of the canister toward the bag end. This situation is most pronounced when the tidal volume of the patient is less than the air space in the canister. The soda lime at the inlet becomes exhausted while that at the outlet remains active. The intergranular and pore air space at the outlet, after a time, is converted to dead space, since the gases are rebreathed without being freed of carbon dioxide. Such a progressive extension of dead space occurs during shallow breathing and during anesthesia for small adults or children when using large or standard size canisters. Smaller canisters, such as the 6×8 or 7×12 cm. sizes, should be employed in sub-

jects with low tidal volumes for more efficient absorption. This problem of progressive extension of dead space is not present in the circle filter since the pattern of absorption differs and tidal volumes less than canister air space do not produce dead space.

EFFECT OF ABSORBENTS ON STABILITY OF ANESTHETIC AGENTS

All inhalational anesthetics are stable in the presence of reacting alkalis except trichlorethylene. The writer has studied the effects of the alkalis in soda lime upon ether, vinyl ether, cyclopropane, ethylene and nitrous oxide. Cyclopropane-oxygen mixtures exposed to canister temperatures of 70°C. remained stable and showed no evidence of deterioration. No evidence of polymerization or conversion to propylene was noted. Ethylene and nitrous oxide are stable in the presence of warm alkalis. Ethyl ether ordinarily is oxidized to peroxides by heat in the presence of oxygen. Ethyl ether mixed with oxygen and exposed to temperatures of 65°C. for one hour developed minute traces of aldehydes, the average being 0.00001%. Peroxide formation did not occur during this time. Vinyl ether, likewise, is stable in the presence of warm alkali. Chloroform may be converted to formic acid by alkalis. However, the resulting formic acid is neutralized by the hydroxides and converted to sodium and calcium formate in the canister. Ethyl chloride is an ester of ethyl alcohol and hydrochloric acid. It may, therefore, be hydrolyzed into these products by the alkali. The hydrochloric acid would, of course, be adsorbed by the alkali but the alcohol remains unchanged. The rate of hydrolysis varies. The presence of the alcohol is of no consequence. Halothane,

ethyl vinyl ether, trifluoroethyl vinyl ether, likewise, undergo no change in the closed circuit.

Trichlorethylene undergoes chemical changes when in contact with warm alkali. It should, therefore, never be used in closed circuit anesthesia with alkaline absorbents. Some oxidation to phosgene occurs. However, the more dangerous product is dichloracetylene which is both neurotoxic and explosive. Dichloracetylene does not form and exert its deleterious effect immediately upon contact with the alkali. Instead, the trichlorethylene is absorbed by the granules and the dichloracetylene forms gradually. The patient exhaling the trichlorethylene usually suffers no ill-effects. It is the one who is anesthetized later who does. Increasing the alcohol content of chloroform, ether or vinethene does not influence the aldehyde or peroxide content of the vapors in a closed system. The possibility that soda lime may act as a catalytic agent and cause flammable organic substances to undergo spontaneous combustion in a closed system has been suggested. This is merely conjecture and no evidence exists that this is so. The possibility of its occurrence seems remote.

BACTERICIDAL ACTION OF ALKALIS

Cross infection from patient to patient by means of the anesthesia apparatus is a problem which has not been satisfactorily solved. This danger may be eliminated by cleaning tubing, masks and connecting pieces thoroughly after use. They are readily detached for this purpose. The canister containing the absorbent is not easily cleaned. Autoclaving is not desirable because of the possibility of disturbing the absorptive power of soda lime or Baralyme. There is strong evidence that no transmission of bacteria occurs from the absorbent. In the laboratory Stoval, Adriani and others have shown that there is no transmission of organisms heavily contaminated with colon, tubercle and other bacilli. The highly caustic nature of the agent and the heat formed during absorption possibly have a germicidal effect. One can, therefore, use a canister on successive cases without fear of transmitting bacterial infection should unsuspected infection be present. Obviously, whatever germicidal properties soda lime may possess are of no benefit in preventing bacteria on breathing tubes, on valves or other portions of the inhaler from passing through. Magath showed that a water trap interposed between the mask and the canister filters bacteria. However, the water trap was found to be impractical because it was cumbersome and introduced resistance. In suspected cases of contamination it is necessary to sterilize the entire inhaler and, in the interest of safety, to discard the soda lime.

The Chemistry of Inorganic Gases

AIR

COMPOSITION

TABLES of the composition of air frequently vary. Discrepancies are due to variations in methods of analysis or methods of expression of quantities.

The composition of air expressed as per cent by weight differs from that indicated by per cent by volume. If expressed by weight, the nitrogen content of dry air is 75.53% and that of oxygen is 23.02%, instead of 78.03% and 20.99%, by volume respectively. The composition in volumes per cent of this complex mixture is summarized in Table I.6. The elements, argon, neon, helium, krypton, and xenon, usually referred to as *the rare gases*, occur in very minute amounts. The rare gases were once believed to be essential to life. This conclusion was drawn from an incorrectly performed experiment in which exhaled carbon dioxide was not removed and killed the animals under observation.

TABLE I.6

THE COMPOSITION OF AIR IN VOLUMES
PER CENT

Nitrogen...	78.03%
Oxygen...	20.99%
Argon...	0.93%
Carbon Dioxide...	0.03%
Hydrogen...	0.01%
Neon...	0.0015%
Helium...	0.0005%
Krypton	0.000005%
Xenon...	0.0000006%

Ozone (O_3) is frequently present in the air in minute amounts after thunderstorms. It also forms when electrical equipment sparks. Dust and bacteria may also be present in amounts which vary with the locality. The moisture content of air is extremely variable.

PROPERTIES

The density of air is 1.84 gms. per liter. The molecular weight is 29.97; the specific heat 0.24 calories per gram. The solubility in water is 2.0 ml. per 100 ml. at 20°C. The relative viscosity compared to water at 20°C. is 0.018. Air may be liquefied. The critical temperature is –141°C. at 37 atmospheres. Liquid air is bluish in color. It possesses some magnetic qualities due to the fact that oxygen is paramagnetic.

LIQUID AIR

Liquid air is the chief source of commercial oxygen, nitrogen, and some of the rare gases. Commercially it is prepared by pressure and cooling. The compression of air to a liquid results in a considerable shrinkage of volume. One cubic foot of liquid air produces 792 cubic feet of free air at atmospheric pressure (20°C. and ordinary room temperature). The cooling during the liquefaction processes is due to the Joule-Thomson effect. Air, at 100 atmospheres pressure and ordinary temperature, when allowed to re-expand to one atmosphere pressure, becomes approximately 25°C. cooler. Air must be cooled in order to be liquefied by pressure because the critical
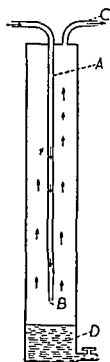
FIG. 1.6. Liquid Air Machine (Linde). Air under pressure enters into tube A and re-expands passing through the nozzle B, becoming cooled during the reexpansion. The cooled air moves upward and out through C causing tube A to become cooled. Thus each succeeding volume of incoming air is cooled by that going out. Eventually a temperature is attained in the system at which air liquefies. Liquid accumulates at D.

Two processes are in use in the manufacture of liquid air—the *Linde* and the *Claude*. In the Linde process a pressure of 200 atmospheres is necessary to accomplish liquefaction, since the cooling must be obtained by allowing the compressed air to re-expand to atmospheric pressure. In the Claude process the air is compressed and is allowed to pass through an orifice into a cylinder head to work a piston. The expanding gas acts
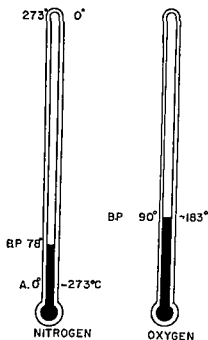
FIG. 2.6. Nitrogen is more volatile than oxygen

temperatures of the gases composing it are far below room temperature. Liquid air boils at such a low temperature that the ordinary methods of cooling are ineffective for liquefaction. The cooling is accomplished by allowing compressed air to pass through a narrow orifice. As it does so it becomes cooled. The cooled, expanded air is then guided around the inlet for the incoming gases. These are cooled in turn (Fig. 1.6). Ultimately, the incoming gases are cooled to a temperature at which they are liquefiable by pressure.

upon the piston and compresses additional fresh air. The cooling is thus obtained in two ways; by the Joule-Thomson effect, as in the Linde process, and by performing external work by compressing the piston. Liquefaction is accomplished at 30 atmospheres pressure and in a shorter time by this process. When liquid air evaporates nitrogen boils off first; the oxygen boils off afterward. (Fig. 2.6.)

OXYGEN

HISTORY

Oxygen was first prepared by Stephen Hales in 1727, but he did not recognize it as an element. The gas was later isolated again by Priestly in 1774 from mercuric oxide and by Scheele in 1775, each man working independently of the other. Lavoisier duplicated Priestly's experiments and noted that the element combined with sulphur, carbon, phosphorus, and other non-metals. The combination of oxygen with other substances was believed by Stahl (1717) to be due to the release of *phlogiston*, which was contained *as an invisible weightless substance in combustible materials.* The residue or ash was supposed to be the original substance minus the phlogiston. The phlogiston theory retarded the studies and discovery of oxygen.

PROPERTIES

Oxygen is tasteless, colorless, and odorless. The gas condenses to a liquid at −119°C. *at 50 atmospheres pressure.* The liquid boils at −183°C. at ordinary atmospheric pressure. The boiling point is higher than that of nitrogen (Fig. 2.6). The specific gravity of the gas (air = 1) is 1.105. The specific gravity of liquid oxygen is 1.14. The density of the gas *is 1.429 gm. per liter at standard conditions.* The liquid may be cooled to a solid which melts at −218°C. The specific heat of the gas is 0.0003 calories per ml. and 0.22 calories per gram. The molecule of oxygen is diatomic under ordinary circumstances and has a molecular weight of 32 (H = 1.006). *The atoms are held together by a double bond.* Oxygen possesses several isotopes. The relative viscosity is 0.020 at 20°C. compared to water. Solubilities are listed later on.

REACTIVITY

The element is highly reactive and combines with many elements to form *oxides, peroxides and suboxides. It has a* negative valence of two. Oxygen supports combustion but cannot be ignited. Oxidizable substances such as cloth, wool, or rubber must be present for oxidation to occur. *If an electric current is passed through oxygen, ozone (O_3) forms in small amounts.*

PREPARATION

From Peroxides

Oxygen was originally prepared for *medical purposes by interacting fused*
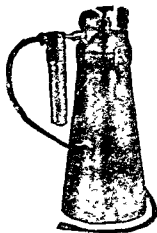
FIG. 3.6. The "oxone" generator used to generate oxygen for clinical use from sodium peroxide. (*Courtesy of Richard Foregger, Ph.D.*)

sodium peroxide with water in a device known as the "oxone" generator (Fig. 3.6). The following reaction illustrates *its formation:*

$$2Na_2O_2 + 2H_2O \rightarrow 4NaOH + O_2 \uparrow$$
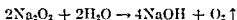
Even on a small scale this method of *preparing oxygen is cumbersome and expensive.*

The modern commercial method of preparation is by fractional distillation of liquid air. Nitrogen, which boils at a

higher temperature than oxygen, evaporates and liquid oxygen remains as a residue.

By Electrolysis

A less popular method employs electrolysis. An electric current is passed through water containing a trace of mineral acid which facilitates conduction. Oxygen, which is electronegative, collects at the anode and hydrogen, which is electropositive, at the cathode. This method is usually used to make hydrogen. Oxygen is merely a by-product but is collected, nevertheless. The reaction may be expressed as follows:

$$2H_2O - 2H_2 + O_2$$
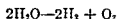
It can be seen that two volumes of hydrogen form for each volume of oxygen. This equation is used to illustrate the law of definite proportions.

By the LeBrin Process

An older process known as the Le-Brin process was first used to prepare oxygen from atmospheric air. Barium oxide (BaO) is heated in air to red heat (500°C.) to form barium peroxide (BaO$_2$). The oxygen is then liberated by raising the temperature to 800°C. Barium peroxide heated strongly to a white heat decomposes into the barium oxide and oxygen. The process is then repeated as often as desired. The reaction is as follows:

$$2BaO + O_2 \rightleftharpoons 2BaO_2$$
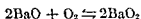
Laboratory Methods of Preparation

Numerous laboratory methods for the preparation of oxygen are available but are of no practical or commercial value. The most common laboratory method of preparation is to heat potassium chlorate

in the presence of a catalyst, such as manganese dioxide.

$$2KClO_3 \xrightarrow{\text{Heat}} 2KCl + 3O_2$$
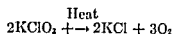
Mercuric oxide, HgO, may be heated to form mercury and oxygen. Priestly liberated oxygen from mercuric oxide by concentrating the sun's rays upon it with a magnifying glass.

$$2HgO \xrightarrow{\underset{\downarrow}{\text{Heat}}} 2Hg + O_2$$
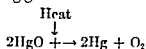
SOLUBILITY

Oxygen possesses a certain degree of water solubility. This fact is of extreme importance in physiology. At 0°C., the water solubility is 4.9 ml. per 100 ml. Were it not for this water solubility, aquatic life would not survive. The solubility of most gases decreases as the temperature rises. Oxygen is no exception to this rule. At 20°C., 3.1 ml. dissolves per 100 ml.; at 40°C., 2.3 ml. In blood, oxygen exists in two forms—combined with hemoglobin in the cell, and in simple solution in the plasma. The amount in simple solution in plasma is less than one would find in pure water under similar conditions because of the presence of electrolytes and other dissolved substances. The amount dissolved in blood when the partial pressure of oxygen in the alveoli is 100 mm. Hg and an equilibrium exists between arterial blood and alveolar air is 100/760 of 2.3 ml., or 0.3 ml. per 100 ml., assuming the solubility in the plasma to be the same as in distilled water. The actual solubility of oxygen in arterial blood of a subject breathing air is 0.24 ml. per 100 ml. at 37°C. The dissolved oxygen in blood amounts to approximately 1% of the total content. Each molecule of hemoglobin combines with as many as

four molecules of oxygen (see Chap. 28). The reaction is expressed as follows:

$$Hb_4 + 4O_2 \leftrightharpoons Hb_4O_8$$
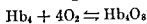
The ferrous iron in hemoglobin is hexacovalent. It, thus, is able to combine with six atoms. Four of these links are utilized for attachment to the nitrogen atoms of the porphyrin ring, one to the globin and one for the oxygen atom. The oxygen, thus, is stabilized and cannot act as an oxidizing agent to convert the iron to the ferric state.

TRANSPORT IN BLOOD

One gram of hemoglobin combines with 1.34 ml. of oxygen. Inasmuch as the normal hemoglobin content averages 15 gm. per 100 ml., of blood, the usual oxygen content of arterial blood averages approximately 19.3 volumes per cent. Venous blood contains less oxygen than arterial although the amount varies with the tissue from which the blood returns. If 100% oxygen is inhaled the partial pressure in the alveoli is increased approximately four times. The portion which combines with hemoglobin is very slightly increased since hemoglobin is normally 95% saturated. However, the amount dissolved in plasma is increased approximately four times. This increased solubility in plasma assumes importance in certain diseases, as for example anaerobic infections, where it is advantageous to saturate the tissues with the gas. The total content is raised to approximately 22.2 volumes per cent. This increase of 10 to 15% is due almost entirely to the increase in dissolved oxygen.

MEDICINAL VERSUS COMMERCIAL OXYGEN

Oxygen is available in two grades, *medicinal* and *commercial*. No signifi-

cant difference exists between medicinal oxygen and commercial oxygen if the latter is pure. Oxygen for acetylene welding must be 99.3% pure to be effective. The U.S.P. requires that oxygen for medicinal purposes have a minimum of 98% oxygen. The remaining gas is usually nitrogen.

STORAGE

Oxygen, as stored for use in anesthesiology, is a gas compressed to a pressure of approximately 2000 lbs. per square inch in cylinders of varying size. Since oxygen liquefies at a high pressure and a low temperature, it exists as a compressed gas in storage cylinders. Liquid oxygen is now being introduced into clinical medicine to permit the transport of quantities in bulk for piping systems. The liquid is transported to the point of utilization and stored in open thermos jugs. These thermos containers consist of a double walled, steel, evacuated container. The evaporating gas is used to fill cylinders in plants where the gas is used in large amounts or it is fed directly into pipe line systems. About 5% of the liquid is lost by evaporation each day. These jugs must be left open to avoid building up an excessive pressure in the container which would result if they were sealed. This loss goes on irrespective of whether or not the gas is being used.

ANALYTICAL METHODS

Physical

The quantitative estimation of oxygen is of importance in clinical medicine, particularly in inhalation therapy. The simplest method of quantitative analysis embodies the use of the Beckman Analyzer which utilizes the Pauling prin-

ciple. This is based upon the fact that oxygen is paramagnetic. This is a physical method which is described in detail in Chapter 7.

Chemical

Although a number of chemical methods are available, the analysis of mixed gas samples is best accomplished by use of the Orsat type of apparatus. Samples of 50 to 100 ml. may be determined to an accuracy of 0.1%. Methods of combustion are sometimes used, but not for clinical purposes. The analysis of gases in liquids is best accomplished either by using the volumetric apparatus of Van Slyke or the manometric apparatus of Van Slyke and Neill or the Scholander apparatus.

The quantitative estimation of oxygen for clinical purposes, particularly in tents, does not require the usual precision and degree of accuracy required of laboratory and research studies. Accuracy is to a certain extent sacrificed for simplicity. Besides the Beckman Analyzer the usual apparatus for oxygen estimation for clinical use is of the Orsat type (Fig. 4.6) with a burette of 10 cc. capacity and one absorption pipette. Water or mercury is used as the displacing medium. The absorption pipette is filled with one of the oxygen-absorbing reagents which is described below. Results are expressed in volumes per cent. Some analyzers are constructed with a syringe-type of burette in which the glass plunger acts in place of the displacement medium.

ABSORBING REAGENTS

Winkler's Solution

The chemicals in the reagent combine with the oxygen to form nonvolatile substances so that a shrinkage of volume
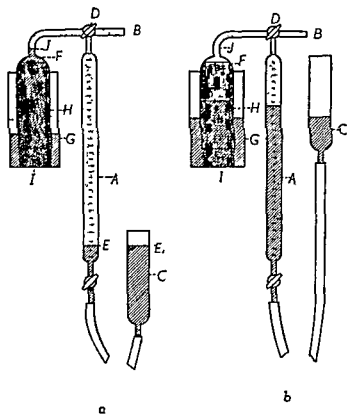
Fig. 4.6. (a) Shows a simple apparatus for the volumetric analysis of oxygen. The sample is drawn into burette A through inlet B by lowering the level bulb C until E and E_1 are at the same level at the zero point. (b) Shows the sample being transferred to the absorption pipette through stopcock D by raising the leveling bulb C. The reagent H is displaced to the outer container of the absorption pipette. The copper wire screen I is necessary if the copper-ammonia reagent is used. At the completion of the absorption the reagent in the absorption chamber is drawn to the zero point J, E and E_1 are adjusted to the same level to have the residual gas at atmospheric pressure.

a   b

occurs. One of the most commonly used chemical absorbents in pyrogallic acid (1, 2, 3 trihydroxybenzene). Hydroxybenzenes are phenols. Phenols, as a rule, are readily oxidized to substances known as quinones. These are dark brown and are objectionable because of their tendency to stain furniture and utensils. Pyrogallic acid is used in the form of *Winkler's Solution*. This is prepared by dissolving 50 grams of the acid in 100 ml. of 30% aqueous potassium hydroxide solution and allowing it to stand overnight away from air.

Badger's Solution

Another commonly used reagent, particularly adaptable for clinical use, takes advantage of the ease in which copper and certain cuprous compounds combine with oxygen. Copper forms two series of compounds—those yielding derivatives with a monovalent ion (cuprous compounds (Cu^+), and those yielding compounds with a divalent ion (cupric compounds (Cu^{++}). The cuprous ion is colorless but in the presence of air and moisture is converted to the cupric ion which is blue. Various hydroxides form in this oxidation which are soluble in ammonium hydroxide and form complex copper-ammonium ions $[Cu(NH_3)_4]^{++}$— (cupric tetramine ion.) Metallic copper is oxidized to cupric oxide if exposed to oxygen. The oxide is dissolved from the surface by ammonium hydroxide which converts it to the cupric ammonium complex. *Badger's Solution* is the preparation most commonly used. This consists of a mixture of half-saturated ammonium hydroxide solution saturated with ammonium chloride. A copper screen, designed to have as extensive a surface as possible, is placed in the absorption pipette. The sample is drawn into the pipette and exposed to the cop-

per screen which is quickly oxidized by the oxygen. The solution, which is colorless when freshly prepared, soon turns blue due to the formation of the cupric ammonium ions. Copper solutions are widely used clinically for oxygen absorption because they are stable, easy to handle, cheap, efficient, and non-destructive if spilled.

Hydrosulphites

A third type of reagent is based upon the fact that sulphites are easily converted to sulphates by oxygen. Sodium hydrosulphite, or sodium sulphoxylate ($Na_2S_2O_4$), is oxidized to sodium bisulphite and sodium bisulphate by oxygen in the presence of moisture.

$$Na_2S_2O_4 + 2O_2 + H_2O \rightarrow NaHSO_3 + NaHSO_4$$
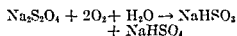
The reagent is a grey-white powder which is dissolved in sodium hydroxide solution (10 gm. in 50 ml. of 1.0 N solution). Sodium anthraquinone beta sulphonate, which is often added as a catalyst to facilitate the reaction, imparts a red color to the solution. When the sodium hydrosulphite is completely converted to the oxidized products the color of this solution turns yellow due to the fact that the solution becomes acid in reaction. This reagent is the one most satisfactory for use in the Van Slyke apparatus for analyzing oxygen in blood and body fluids.

OXYGEN TENSION IN TISSUES

Oxygen tension in the tissues may be determined by use of polarographic methods. *Polarography* is essentially electrolysis of dilute solutions containing reductible or oxidizable substances. When a voltage is applied to electrodes immersed in a solution containing oxy-

gen, the oxygen is reduced, that is, it takes up electrons. The transfer of electrons is a function of the amount of current flowing which depends upon the oxygen concentration. This voltage is measured by a galvanometer and translated into terms of oxygen tension. (See Chap. 36.)

OXIMETRY

Blood oxygen saturation may be determined on a moment to moment basis using the ear oximeter devised by Millikan. This apparatus, also called the Oxyhemograph, operates as follows:

A lamp of constant intensity delivers red light through the pina of the ear. Oxyhemoglobin absorbs red light whose wave length is 6400 A. Reduced hemoglobin absorbs none. Both oxyhemoglobin and reduced hemoglobin absorb red light whose wave length is 8000Å, however. Therefore, a light source which provides red light of both wave lengths is used. The rays of light traverse the pina and, after passing through appropriate filters, fall on two separate photoelectric cells each of which responds to 6400 A wave length and the 8000 A respectively but not to the other. The ratio of the amount of transmission of each type is measured by determining the degree of electrical activity set up in each photoelectric cell with galvanometers. This ratio is translated into terms of percent saturation. This device merely indicates changes from a control level and is not suitable for establishing absolute values. The apparatus must be standardized using the Van Slyke or Scholander gas analyzer. The percent of error is appreciable when the skin is heavily pigmented, when blood oxygen values are low and when blood flow tends to be variable or slow.

DIFFUSION

Coryllos and Birnbaum, and other workers subsequent to them, found that oxygen rapidly diffuses from the alveoli of a lung lobule which has its bronchus occluded. Nitrogen and helium and other inert gases diffuse far more slowly under similar circumstances. Oxygen diffuses in 15 minutes in contrast to nitrogen which requires 16 hours under comparable conditions.

OXYGEN TOXICITY

The inhalation of oxygen rich mixtures over long periods of time—24 to 36 hours or more—causes pulmonary irritation and other symptoms of toxicity. The inhalation of oxygen under pressure results in serious symptoms such as disturbances of sensorium, disorientation and convulsions within 30 minutes or sooner. The exact mechanism of causation is not understood. Presumably the elevated plasma oxygen level, which at 5 atmospheres may be 6 volumes percent, or more, meets the metabolic oxygen requirement. The amount of oxygen released from hemoglobin, therefore, is only a fraction of that which occurs at atmospheric pressure. The hemoglobin, therefore, has less capacity for carbon dioxide transport. The carbon dioxide tension in tissues and plasma is increased. This in turn increases the blood flow through the brain. Possibly the excess oxygen also interferes with enzymatic activity in the brain.

NITROGEN

HISTORY

Nitrogen was first isolated by Daniel Rutherford in 1772. Nitrogen is an inert element which combines with other elements with difficulty and under unusual circumstances. For this reason, it is a

valuable diluent and quenching agent for anesthesia.

PREPARATION

Commercially, nitrogen is prepared by the fractional distillation of liquid air. Actually it is a by-product of the manufacture of oxygen. Nitrogen passes off first since it is more volatile than oxygen (B.P. —195°C.) The gas may be prepared in the laboratory by heating ammonium nitrite.

$$NH_4NO_2 + Heat \rightarrow N_2 \uparrow + 2H_2O$$
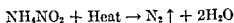
Nitrogen requires a high pressure and a low temperature for liquefaction. It, therefore, is dispensed as a compressed gas in storage cylinders and not as a liquid. The critical temperature is —147°C. and the critical pressure is 33 atmospheres.

PROPERTIES

The gas is tasteless, colorless and odorless. The atomic weight of nitrogen is 14.005. At least two isotopes of nitrogen exist. The molecule is diatomic, therefore, its molecular weight is 28.016. The two atoms are held together by a triple bond which accounts for its inertness (:N:::N:) The gas is lighter than air and has a specific gravity of 0.967 (air = 1). The density is 1.205 gm. per liter at standard conditions. The specific heat is 0.0003 calories per ml. and 0.25 calories per gram. The relative viscosity compared to water (1.0) is 0.017 at 20°C. The liquid solidifies at —209.8°C.

REACTIVITY

Nitrogen unites with other elements with difficulty. The nitrogen atom has a small radius. The electrons approach the nucleus closely and are, therefore,

strongly held to it. A molecule of nitrogen exerts little attraction on neighboring molecules. As a result nitrogen liquefies and solidifies at a very low temperature. It is superseded only by hydrogen and helium in this respect.

Nitrogen combines with hydrogen to form ammonia if an electric spark is passed through a mixture of the gases at high pressure. Nitrogen also combines with oxygen under the influence of pressure and electric sparks to form a mixture of oxides. Five oxides of nitrogen are possible. Nitrogen monoxide, or nitrous oxide, the lowest member of the series and the least toxic of the five, is well known for its anesthetic properties. The oxides of nitrogen are anhydrides of various acids. Nitric oxide (NO) is a poisonous substance which is of interest because it may be present as an impurity in nitrous oxide. Nitric oxide combines with water to form a mixture of nitric and nitrous acids. Nitrogen tetroxide (N_2O_4) is a brown gas which forms when nitric oxide combines with oxygen. Nitric oxide, which is a colorless gas, forms when nitric acid reacts with metals. The gas combines with the oxygen in air to form the brown nitrogen tetroxide. Nitrogen trioxide (N_2O_3) is the anhydride of nitrous acid (HNO_2). Nitrogen pentoxide (N_2O_5) is the anhydride of nitric acid (HNO_3). The oxides of nitrogen, therefore, with the exception of nitrous oxide, are extremely toxic, acid-forming substances, and of no clinical value. If inhaled, they react with the water in the tissues to form their respective acids which irritate the pulmonary epithelium.

DISTRIBUTION IN CELLS

Nitrogen is an essential element as far as life is concerned since it is a necessary constituent of proteins and other body

substances. However, it can only be obtained from the atmosphere through the action of nitrifying bacteria or by plants able to convert atmospheric nitrogen into organic nitrogenous products. Atmospheric nitrogen, even though it is inert, is essential as a diluent for oxygen. The inhalation of high concentrations of oxygen for protracted periods produces signs of toxicity.

DISTRIBUTION IN THE BODY

Nitrogen plays an important part in physiology and anesthesia. At 0°C. and 760 mm. Hg pressure 2.4 ml. dissolve per 100 ml. of distilled water. The solubility of the gas decreases as the temperature rises. Nitrogen, because of its small attraction for other molecules, as one would predict from this fact, is poorly soluble. Enough dissolves in the blood plasma (1.28 ml. per 100 ml. of water at 37°C.) and body tissues to require consideration in anesthesia and inhalation therapy. Nitrogen does not combine with any particular substances in the blood or tissues. It exists in simple solution only. The diatomic molecules characteristic of the gas persist even into the liquid and solid phases. The solubility of nitrogen in lipoids is greater than it is in water. The coefficient of distribution between oil and water at 37°C. is 3.24. The amount which dissolves in the tissues at increased atmospheric pressure is directly proportional to the atmospheric pressure, according to Henry's Law. The sudden release of this pressure decreases the amount in solution. The gas escapes from the tissues and body fluids and forms minute bubbles giving rise to aeroembolism. These bubbles accumulate in blood and tissues and produce serious symptoms known as the "bends." The severity of the symptoms

depends upon the magnitude of the pressure and the duration of the exposure. The longer the exposure the greater the amount of gas which dissolves in the tissues. The symptoms are more severe in the obese. Symptoms do not appear if the pressure is less than 2 atmospheres. In addition, nitrogen under increased pressure acts as a narcotic because it is inert and a considerable amount dissolves in the lipoid material of the cells (see Helium).

DESATURATION OF TISSUES

Certain anesthetic gases such as nitrous oxide and ethylene require high partial pressures in blood and tissues to be effective. Effective concentrations in the cells can only be obtained by eliminating the nitrogen. The nitrogen in blood and alveoli is eliminated by washout within two minutes (Chap. 5). That which is present in tissues is slowly lost. Complete desaturation may require seven or eight hours. Therefore, even though the blood is almost completely desaturated, the tissues are not necessarily so. The replacement of the nitrogen of the blood by the gas is referred to as "primary saturation." The replacement of the tissue nitrogen by the gas is known as "secondary saturation." The technique, referred to as "secondary saturation," which was once employed to maintain nitrous oxide anesthesia, is essentially an attempt to desaturate the tissues of their dissolved nitrogen. After anesthesia is established with a nitrous oxide-oxygen mixture, the patient is made to inhale 100% nitrous oxide and to exhale through an expiratory valve. This increases the partial pressure of nitrous oxide in blood and favors the diffusion of the nitrogen from the tissues, and conversely the diffusion of nitrous oxide

into the tissues. Oxygen and nitrous oxide-oxygen mixtures are restored when respiratory failure from anoxia appears imminent. Nitrogen desaturation is also employed in inhalation therapy to increase the partial pressure of oxygen in tissues by inhalation of 100% oxygen. Nitrogen diffuses outward into the blood and to the lungs, and thence to the outside air, while oxygen diffuses into the tissues. This procedure is employed for the attempted prevention of aeroembolism in the treatment of anerobic infections, in attempts to decompress hollow viscera of contained nitrogen, and in other clinical conditions where the removal of nitrogen from tissues is advantageous.

An isolated lung lobule filled with nitrogen whose bronchus has been occluded requires approximately 16 hours for the nitrogen to diffuse into the blood and for complete deflation of the lobule. Under similar circumstances, oxygen disappears in 15 minutes. The use of nitrogen as a diluent for quenching purposes is described in Chapter 32.

ANALYTICAL METHODS

The quantitative analysis of nitrogen by chemical methods is not a simple matter by any means. Usually it is measured as a residual gas. In other words, all the other gases in a mixture are absorbed and those which remain are presumed to be nitrogen. A mixture of cyclopropane, oxygen, carbon dioxide and nitrogen can be analyzed on the Orsat. Appropriate absorbents are available for all the gases except nitrogen which remains after the others are absorbed. Nitrogen in blood is determined on the Van Slyke as a residual gas after carbon dioxide and oxygen are absorbed.

Certain physical methods of analysis

are available. The nitrogen meter (Chap. 7) is a physical method of analysis based upon the fact that nitrogen glows with a bright orange pink color if exposed to sufficient electrical excitation. The spectral region is between 3100–4800 Å. A filter interposed between the discharge tube and the photoelectric-cell isolates this band. This device has a fast response so that moment to moment analysis is possible.

Nitrogen may also be analyzed by means of the gas chromatograph and the mass spectrograph.

NITROUS OXIDE

HISTORY

Nitrous oxide, or nitrogen monoxide, is the least toxic and irritating of the five oxides of nitrogen. The substance was first identified by Priestly in 1772. Its anesthetic properties were first demonstrated by Sir Humphrey Davy in 1799. Nitrous oxide is the most extensively used inorganic gas of clinical importance for anesthesia in man.

PROPERTIES

The emperic formula of nitrous oxide is N_2O. The lowest valence of nitrogen is utilized. Its molecular weight is 44.02; its specific gravity 1.527 (air = 1). Nitrous oxide is a colorless gas with a slightly sweet odor and taste. The gas is non-irritating when inhaled. Nitrous oxide compresses at 50 atmospheres pressure at 28°C. to a clear, colorless liquid. The liquid has a specific gravity of 1.226 at its boiling point (−89°C.). The liquid freezes into a solid at −120°C. The critical temperature is −89°C., the critical pressure is 72 atmospheres. The specific heat is 0.0004 calories per ml. and 0.21 calories per gram of gas. The viscosity is 0.014 be-

ing less viscous than air ($H_2O = 1.0$ at $20°C$).

STABILITY

Nitrous oxide is stable under ordinary circumstances. The gas does not decompose or polymerize in the compressed or liquid state if it is stored for any length of time at ordinary temperatures. The substance decomposes into nitrogen and oxygen at $900°C$. The gas is stable in the presence of soda lime mixtures and Baralyme used for carbon dioxide absorption.

SOLUBILITY

Nitrous oxide is very soluble in water. At $20°C$. and 760 mm. Hg, 1.5 volumes dissolve in 1 volume of water. At $37.5°C.$, 0.44 volumes are soluble per unit volume of water; in blood, 0.47 volumes per unit volume; and in oil, 1.46 volumes per unit volume. The oil/water distribution coefficient at $37.5°C$. is 3.2 and the oil/blood distribution coefficient is 3.0. The gas is very soluble in alcohol. During surgical anesthesia, the required inspired concentration of nitrous oxide is between 85 and 92 volumes per cent.

Nitrous oxide is the anhydride of a hypothetical substance, hyponitrous acid ($H_2N_2O_2$). This acid is of theoretical interest. It does not form under ordinary circumstances, as when nitrous oxide is dissolved in water. Solutions of nitrous oxide are neutral to litmus and other indicators.

BLOOD CONCENTRATION

The blood concentration in man during surgical anesthesia varies but averages approximately 23 volumes per cent. The data of various observers are not in agreement due to differences in analytical methods. Cullen and his associates,

using the Van Slyke apparatus and the method of Orcutt and Waters for analysis, found the average nitrous oxide content of blood of patients breathing a mixture $76\%–80\%$ of the gas with oxygen at 760 mm. Hg to be 29 volumes per cent. The average nitrous oxide content of blood rose to 30 volumes per cent when the nitrous oxide content in the inspired mixture was increased to $85\%–88\%$.

PREPARATION

Nitrous oxide is not easily formed by direct combination with oxygen because nitrogen is an inert element, except under unusual conditions. High pressure and the presence of catalysts are necessary for direct union. The combination of nitrogen with oxygen to form nitrous oxide is an *endothermic* reaction.

The most common, and simplest, method of preparation, and the one used commercially involves gentle decomposition of ammonium nitrate by heat. Ammonium nitrate crystals are heated in a retort to $190°C$. until a molten mass results. All fumes and gases formed are discarded before the fusion occurs. The temperature is then raised to $240°C.$, at which point the decomposition occurs. The reaction is expressed by the following equation:

$$NH_4NO_3 + \xrightarrow{\text{Heat}} N_2O + 2H_2O$$
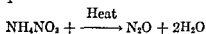
This method of preparation yields approximately 95% nitrous oxide. The remaining gas is mostly nitrogen and its various higher oxides. Priestly prepared small amounts of nitrous oxide by reacting iron with nitric acid. In this reaction nitric oxide (NO), the next higher homologue to nitrous oxide, is first produced. An excess of iron is present which reduces the nitric oxide to nitrous oxide.

$$2NO + Fe \rightarrow FeO + N_2O$$

This laboratory method of preparation is of interest because the principle of reducing nitric oxide to nitrous oxide is used for purification of the product. Victor Meyer (1875) prepared nitrous oxide by heating hydroxylamine. This is probably the source of the purest product, but the method is not practical for commercial use because the initial ingredients are costly.

STORAGE

Nitrous oxide is stored in heavy metal cylinders in liquid form at a pressure which varies with the room temperature. As the liquid evaporates and the gas passes from the cylinder the temperature falls rapidly. Moisture in the gas or around the valves condenses and often freezes. This causes an uneven flow of gas. At one time this was a frequent source of annoyance during clinical anesthesia because moisture was not entirely removed during manufacture and the valves often became obstructed by frozen moisture.

STABILITY

At temperatures above 450°C. the higher oxides of nitrogen may form. Such temperatures may well be attained during liquefaction by compression. In order to obviate this possibility, compression is carried out in three stages with cooling between stages. The first pressure applied does not exceed 100 pounds per square inch; the second, 300 pounds per square inch; and the final pressure, 1000 pounds per square inch. Inasmuch as the product exists as a liquid in the cylinder and the pressure overlying the liquid varies with the room temperature, the reading on a pressure gauge attached to the cylinder is no index to the quantity present. The actual quantity of nitrous

oxide in a cylinder is best determined by weighing the cylinder and its contents and subtracting the weight of the cylinder.

ABSORPTION AND ELIMINATION

Nitrous oxide is eliminated from the body unchanged, largely by way of the lungs. There is a possibility that minute traces of nitric oxide could form in the body. Whether or not a loose combination occurs with hemoglobin is debatable. Suggestions of changes in the spectrograph of hemoglobin have been reported. Most of the evidence supports no combination of the gas with hemoglobin. Nicoloux was unable to detect the gas in venous or arterial blood after five minutes. The drug does not undergo any alteration in tissues. Nitrogen in the lungs and blood must be replaced by nitrous oxide to obtain satisfactory anesthesia.

The blood concentration is reduced to almost zero within several minutes after termination of nitrous oxide anesthesia. Minute amounts circulate for considerable time afterward in the blood but are not detectable by the ordinary methods of analysis. This comes from tissues with a poor blood supply, which, once saturated, are desaturated slowly. Nitrous oxide, like many other anesthetic gases, diffuses very rapidly from an isolated lung lobule filled with the pure gas whose blood supply is intact and whose bronchus is occluded. It was found to disappear in 17 to 35 minutes. Nitrogen requires 16 hours under comparable conditions. The gas also diffuses through the skin of anesthetized subjects in very minute amounts.

IMPURITIES

The present day mode of manufacture

and purification removes both moisture and impurities. The gas is first scrubbed to remove alkaline and acid substances. It is then compressed in stages to remove non-liquefiable gases, such as nitrogen and oxygen. Passage over iron filings removes the higher oxides of nitrogen. The impurities most likely to be present in nitrous oxide are nitrogen, ammonia, the higher oxides of nitrogen—particularly nitric oxide (NO)—and moisture. Nitric oxide, which is the most dangerous impurity, acts in two ways when inhaled. It may combine, as does carbon monoxide, with hemoglobin to form nitric oxide hemoglobin. This prevents the transport of oxygen. Before it reaches the blood, however, it reacts with water to form nitric and nitrous acids. These injure the pulmonary epithelium and cause pulmonary edema. Nitric oxide in a concentration of 780 parts per million of air kills mice and rats in less than 30 minutes. It has been mentioned previously that this impurity is removed by passing the gas over finely-divided iron, whence it is reduced to nitrous oxide.

DETECTION OF IMPURITIES

Nitric oxide may be detected qualitatively by passing a sample of the gas through ferrous sulphate solution ($FeSO_4$). The interaction of these two substances produces a black liquid ($FeSO_4 \cdot NO$) This is a reversible reaction and after a time the color disappears. Likewise, if other higher oxides of nitrogen are suspected to be present, a sample of the gas may be bubbled through a 15 molar potassium iodide solution containing a drop of glacial acetic acid and starch solution. The higher oxides of nitrogen act as oxidizing agents. A blue color results from liberation of free iodine by the oxidizing action of the contaminating agent.

Nitrogen, although an inert substance and not harmful per se, reduces the efficiency of the agent by its diluting effect. The fractional compression method of purifying and packing the gas is also designed to remove nitrogen since the latter is not liquefied at the pressures used.

FLAMMABILITY

Nitrous oxide combines with additional oxygen with utmost difficulty. Therefore, it is non-flammable. Nitrous oxide supports combustion, once combustion has been initiated. A burning splinter thrust into a jar of pure nitrous oxide continues to burn vigorously. The nitrous oxide yields its oxygen to support combustion. Nitrous oxide supports combustion of ether, ethylene, cyclopropane and other flammable organic gases and vapors, should such a mixture be ignited. Oils vaporized in a stream of nitrous oxide under pressure may form explosive mixtures. Hydrogen mixed with nitrous oxide without oxygen can be exploded.

DETECTION AND ANALYSIS

The determination of nitrous oxide by chemical methods is not a simple matter. Nitrous oxide may be determined quantitatively in blood and liquids by use of the manometric apparatus of Van Slyke and Neill. The technique used is similar to that for the determination of cyclopropane and ethylene in the blood as described by Orcutt and Seevers (see Gas Analysis). The gas is determined as a residual gas. A simple chemical method for quantitatively measuring nitrous oxide in a sample of fixed gases was devised by Orcutt and Seevers. This method employs the diazo reaction. It may be used if the specimen contains no nitrogen. The nitrous oxide

is converted to higher nitrogen oxides by heating it with oxygen in the presence of a catalyst of hot porcelain. The oxide is then passed into potassium hydroxide solution to form potassium nitrite. The nitrite, alpha naphthylamine, hydrochloric acid, and sulphanilic acid are allowed to react together. Diazotization occurs and a red dye forms which is compared colorimetrically to a standard prepared with a known quantity of *nitrous oxide (see diazo reaction)*. Nitrogen forms nitrites and interferes with the determination. Inasmuch as nitrogen is difficult to exclude from specimens of gas containing nitrous oxide, the test possesses limited usefulness.

Developments in techniques of analysis of nitrous oxide will be in the line of physical methods. The interferometer has been used for the analysis of nitrous oxide with *some degree of success*. The gas chromatograph and the mass spectrograph lend themselves to the quantitative analysis of the gas in a mixture of gases.

CARBON DIOXIDE

Two oxides of carbon are possible— the monoxide and the dioxide. The monoxide, in which carbon has a valence of 2, is converted to the dioxide in which the valence is 4. The oxidation of carbon is an important source of energy. Both oxides are important, but the dioxide is more important from the standpoint of anesthesiology, since it plays such an important role in biochemistry and the pharmacology of anesthetic drugs. Organic compounds, when completely oxidized, yield carbon dioxide and water.

History

Carbon dioxide was first described by Black in 1757. The gas is a compound of carbon and rightfully belongs among organic compounds, but is usually considered along with inorganic compounds.

Laboratory Preparation

The laboratory preparation of carbon dioxide is simple. Any strong mineral acid added to a carbonate or bicarbonate releases the gas. Sodium bicarbonate and *calcium carbonate are used for preparation most frequently. Carbonic acid first forms. This is volatile and unstable and liberates its anhydride, carbon dioxide.

$$NaHCO_3 + HCl \rightarrow NaCl + H_2O + CO_2$$
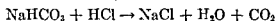
Commercial Preparation

The most common commercial source of carbon dioxide is from kilns and smelters where alkaline earth oxides, particularly those of calcium and magnesium, are prepared from their respective carbonates. The formation from limestone is as follows:

$$CaCO_3 \xrightarrow{\text{Heat}} CaO + CO_2$$
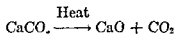
The carbonates of calcium, barium, strontium and magnesium are easily decomposed into *carbon dioxide and the metallic oxide by heat. The gas is then purified. In localities where no kilns are situated, the gas is prepared by the burning of coke and other carbonaceous substances. The gas is passed into aqueous sodium hydroxide to form sodium carbonate which is subsequently decomposed by an acid to liberate a pure carbon dioxide gas.

Vast quantities of carbon dioxide are also recovered during the fermentation of grains in brewing and the manufacture of alcohol. There are a few natural sources of carbon dioxide, such as springs and subterranean caverns leading from the earth.

Distribution

The concentration of carbon dioxide

in the atmosphere is relatively minute—3 parts per 10,000 (0.03%). The estimated total in the entire atmosphere amounts to 2,200,000,000,000 tons. Even though the concentration in the atmosphere is small, the quantity is sufficient to furnish carbon for all plant life.

STABILITY

Carbon dioxide is a very stable chemical substance. An extremely high temperature (9,000°C.) is required to decompose it into carbon and oxygen.

SOLUBILITY

Carbon dioxide is very soluble in water because it combines with it to form carbonic acid. The solubility of carbon dioxide is not in accordance with Henry's Law because of this chemical union. At 20°C. 105 ml. of the gas dissolve in 100 ml. of water. The solubility in pure water at body temperature is 5.45 ml. per 100 ml. The solubility decreases as the temperature increases. One gram dissolves in 300 ml. at 0°C.; while at 25°C. 700 ml. are required. It is less soluble in alcohol and most organic solvents than in water. Carbon dioxide is more soluble in lipoids than water (50% more). Carbon dioxide possesses a pungent odor and in high concentrations is irritating to mucous membranes.

PROPERTIES

The molecular weight of carbon dioxide is 44. The gas is, therefore, heavier than air (specific gravity 1.54, air = 1). The relative viscosity compared to water is 0.015 (air = 0.018). Carbon dioxide is easily compressed by a pressure of 50 atmospheres at 20°C. to a colorless liquid. Inasmuch as the gas possesses a relatively high critical temperature

(31°C.) and low critical pressure (73 atmospheres) it is dispensed and stored as a liquid in cylinders for commercial and medicinal purposes. The density of the liquid is 0.77 gm. per ml. at 20°C. The liquid boils at —78°C. The vapor pressure at 20°C. is 56 atmospheres. The specific heat of the gas is 0.0004 calories per ml. and 0.20 calories per gram of gas. That of the liquid is 0.70 calories per gram. Carbon dioxide is neutralized and absorbed by both weak and strong alkalis to form carbonates. In the presence of an excess of carbon dioxide a carbonate reacts to form the acid carbonate or bicarbonate:

$$Na_2CO_3 + H_2CO_3 \rightarrow 2NaHCO_3$$

USE FOR QUENCHING

Carbon dioxide acts as a quenching agent for flammable mixtures of oxygen and anesthetic gases. This effect is largely due to its high molal heat capacity (Chap. 22). A concentration of approximately 5% markedly decreases the range of flammability even if there is adequate oxygen present to maintain combustion. Carbon dioxide, by virtue of its ability to form an ionizable acid, allegedly aids in the conduction of electricity. Charges of static electricity were once believed to be more easily dissipated due to its presence. This is true when carbon dioxide is present in the atmosphere in concentrations of 0.5% or more. However, the substance is so poorly ionized that the amount normally present in the air plays little, if any, role in the dissipation of static charges. Some students of the problem of "explosions" have felt that there is higher incidence of explosions in air-conditioned operating rooms and that this is due to the removal of all carbon dioxide from the air during the process of dehumidification in the conditioning

unit. There is little evidence to support this.

ANALYSIS

Carbon dioxide may be detected *qualitatively* in air or gas mixtures by passing a sample of gas through a concentrated solution of filtered calcium or barium hydroxide. A white cloud composed of a very fine precipitate of the highly insoluble carbonates of calcium or barium appears. This is a highly sensitive test. Indicators are often used to determine whether or not carbon dioxide is present in a sample of gas. Such indicators as phenol red or bromcresol purple change color due to the fact that carbon dioxide forms carbonic acid with water.

Carbon dioxide may be estimated *quantitatively* in samples of gases by use of some absorptiometric technique in the Haldane, Orsat type or similar type of apparatus (Chap. 7). A 30% solution of potassium hydroxide is an effective absorbent. Small samples containing minute quantities of carbon dioxide may be analyzed with the manometric apparatus of Van Slyke and Neill or the Scholander.

The gas may be analyzed quantitatively in blood and other tissue fluids on the volumetric apparatus of Van Slyke, the manometric apparatus of Van Slyke and Neill or by use of the Scholander apparatus. In the Van Slyke techniques the liquid is first extracted in a vacuum in an acid medium which decomposes the carbonates, bicarbonates and carbamino compounds. In both the volumetric and manometric techniques the extracted gases are compressed to a given volume and carbon dioxide is absorbed by means of potassium hydroxide. The volume of carbon dioxide, or volumes per cent, is

then calculated from the differences in reading before and after absorption. In analysis of a mixture of gases, it is customary to remove carbon dioxide first. In oxygen analysis, carbon dioxide must be removed first because reagents used to absorb oxygen are alkaline and absorb carbon dioxide along with the oxygen.

Physical methods of detection are more widely employed than chemical for continuous sampling. The Liston-Becker apparatus (also Beckman-Spinco), based upon the fact that carbon dioxide absorbs infrared rays, is used extensively in anesthesia and physiological research (Chap. 7).

CARBON DIOXIDE OUTPUT

Satisfactory provisions for removal or escape of carbon dioxide from rebreathing appliances must be made; otherwise toxic responses must ensue. The minute to minute output varies with the degree of activity, metabolic rate, and respiratory quotient of the subject. Assuming the respiratory quotient to be 1, the output per minute is equivalent to the oxygen consumption. An adult at rest breathes approximately 600 liters of air, uses 18–20 liters of oxygen and exhales approximately 18 liters of carbon dioxide per hour. During anesthesia the carbon dioxide output is decreased. The average output in an adult is 200 ml. per minute. The average per cent in the expired air may be 4 per cent or more even though the output is decreased because ventilation is diminished.

CARBON DIOXIDE-OXYGEN MIXTURES

Carbon dioxide-oxygen mixtures used for inhalation therapy are prepared by introducing the carbon dioxide into the cylinder first, and then adding the oxygen. These mixtures are sometime re-

ferred to as a "Carbogen." Mixtures are required to be accurate to 0.1% by the U. S. Pharmacopoeia. Stratification may occur when the two gases under pressure are mixed together. However, amounts up to 30% carbon dioxide may be mixed with oxygen without stratification at room temperatures. These mixtures remain homogeneous. Mixtures with more than 30% must be formed by the use of separate flow meters and combining the necessary volumes at the time of use of the mixture.

Solid carbon dioxide is impractical to use for inhalation therapy. Carbon dioxide is included in the U.S.P.

THE RARE GASES

CHEMICAL ACTIVITY

The group of elements at the extreme right of the periodic table are often referred to as the "rare gases." This group, each member of which is inert, consists of neon, xenon, krypton, argon, and helium. All are found in air and none, as far as is known, is essential to life. The atoms of these elements have no valence electrons. These substances, therefore, combine with no other element except under very unusual circumstances. Their interest in anesthesiology is due to their gaseous nature and their chemical inertness. Helium is used as a diluent and quenching agent in gas mixtures. Krypton and xenon possess a degree of lipoid solubility comparable to some anesthetics.

DISTRIBUTION

Argon is the most abundant of the rare gases. If molecules of air were to pass a given point at the rate of one per second an argon molecule would pass every two minutes, a krypton molecule every eight months, a xenon molecule every five years.

The inertness of these gases is not absolute, however. Krypton, xenon and argon form unstable hydrates. Argon combines with brom-trifluoride to form unstable compounds. In spite of their inertness they may cause some degree of narcosis. This property decreases in the following order: xenon, krypton, neon, argon and helium.

HELIUM

DISTRIBUTION

The most frequently used of these gases for clinical purposes is helium (He). Helium was noted in the spectrum of the sun during an eclipse by Janssen in 1868. It was isolated from uranitite in 1895 by Ramsay. The name of the element is derived from the Greek word *helios* which means sun. The chief source of helium is from the natural gases of the oil wells of Kansas and Texas which contain from 0.01 to 2% of the element. The other gases, which are chiefly hydrocarbons, nitrogen and oxygen, are removed by absorption, liquefaction, or scrubbing with water and sodium hydroxide. The temperature, then, is lowered to $-195°C$. The helium, which is difficult to liquefy, remains as a gaseous residue. The other gases either liquefy or are adsorbed by activated charcoal. Helium is also the end-product of the disintegration of radium and other radioactive elements.

PROPERTIES

Helium is the second lightest element known, being second to hydrogen in lightness. The molecule of helium is monatomic. The atom and the molecule, therefore, have the same atomic and

molecular weight (4.002). The atomic number is 2. Helium is twice as heavy as molecular hydrogen. The density of helium is 0.177 gm. per liter. The buoyant effect of helium is well recognized. Only hydrogen is superior in this respect. The gas is tasteless, colorless, and odorless. Helium liquefies at an unusually low temperature (−268.9°C.). The pressure required for liquefaction, however, is of small magnitude, being only 2.26 atmospheres. The element solidifies at −272.2°C. This is one of the lowest temperatures which has ever been attained, approximating almost absolute zero. Helium is the most difficult substance to liquefy and solidify pressure being required regardless of temperature. The specific heat of the gas is 0.0002 calories per ml. and 1.25 calories per gram.

An electrical discharge through mercury vapor and helium mixture forms two unstable complexes, HgHe and HgHe₂.

IMPORTANCE OF SOLUBILITY

Helium is the least soluble of the *elemental* gases. Sulphur hexafluoride is less soluble than helium. The water solubility is 0.87 ml. per 100 ml. at 37°C. The olive oil solubility is 1.48 ml. at 37°C. It has a low oil/water ratio (0.187 at 37°C.) and for this reason has been advocated for inhalation, particularly by divers who are subjected to increased atmospheric pressure. The nitrogen in the cells is replaced by helium, but since the solubility of helium in blood and lipoids is less than that of nitrogen, the narcotic effects characteristic of inert gases under these circumstances is minimized. In addition, aeroembolism due to the bubble formation during decompression is less of a problem.

PHYSICAL BASIS FOR CLINICAL USES

Helium has also been used as a replacement gas for encephalography and in cases of respiratory obstruction. The gas is not only useful because of its inertness and low water and lipoid solubility but also because of its lightness. A mixture of 21% helium and 79% air has a specific gravity of 0.341. Relatively speaking, then, it is almost one-third as heavy as air. It diffuses faster and with greater ease through narrowed orifices. Helium is ⅛ as heavy as oxygen and, therefore, according to Graham's Law diffuses 2.8 times faster. The gas is used as a diluent with oxygen in cases of chronic obstructions of the respiratory tract. The mechanical advantage is increased due to the low specific gravity. The effort required to move the tidal volume of helium-oxygen mixture is approximately one-third that required to move air under similar circumstances. A mixture of 60% helium, 25% oxygen, and 15% cyclopropane has a specific gravity of 0.558. The force required to move it is about one-half of that required for a mixture of 85% oxygen and 15% cyclopropane, which has a specific gravity of 1.16.

VISCOSITY

The relative viscosity of helium at 20°C. is 0.019 (H₂O = 1).

ABSORPTION AND DIFFUSION

The gas is absorbed extremely slowly from the alveoli of a lung lobule with an intact blood supply but whose bronchus is occluded because of its low water solubility. The diffusion of nitrogen requires 16 hours while helium, under similar circumstances, requires 26. The gas has been used at the termination of anesthesia as a prophylactic measure to prevent atelectasis. There is

no rational basis for this procedure since the helium is immediately replaced by air when inhalation is discontinued if the bronchus is patent. Should the helium be trapped, collapse will be delayed but not prevented. Helium, as do nitrous oxide, ethylene, and other gases, diffuses through the skin in minute quantities. Helium readily diffuses through rubber, and even through glass. The speed of sound is increased as the density through which it is travelling is decreased. The voice of a patient inhaling helium becomes higher pitched than normal because the vocal cords vibrate at a more rapid rate than they do when air is inhaled. In addition, it assumes a nasal twang because the sinuses and other cavities are filled with the gas.

QUENCHING EFFECT

Helium possesses a high degree of heat conductivity. It is thus capable of cooling sparks, thereby acting as a quenching agent. If added to mixtures of flammable anesthetics the limits of flammability are decreased. A mixture of 50% cyclopropane with 12% or more helium combined with oxygen does not ignite. Similar reduction in flammability occurs with ether, helium and oxygen mixtures.

ANALYSIS

The quantitative determination of helium is difficult since it is chemically inert and combines with no substance to form stable compounds. Therefore, in volumetric determinations, it must be measured as a residual gas after the other gases are absorbed. Gases and vapors are readily adsorbed to activated surfaces such as charcoal or silica gel at room temperatures if they are derived from liquids having relatively high boiling points. Gases derived from liquids

which boil at low temperatures are not readily adsorbed at room temperatures but may be at low temperatures. Helium, however, is not adsorbed by activated charcoal even at very low temperatures. The other gases with which it occurs are, however. Therefore, in the quantitative determination of helium, the gas mixture is cooled to an extremely low temperature ($-195°C.$) and treated with activated charcoal which adsorbs all substances except helium whose volume is then measured. This analytical technique may be executed by means of the manometric apparatus by Van Slyke and Neill. Boothby and his coworkers devised a method to measure the composition of oxygen, nitrogen, helium mixtures by measuring the speed of sound through the mixture. This technique is used by some workers (Chap. 7).

XENON

DISTRIBUTION

Xenon (Xe) is one of the few inorganic substances which produces general anesthesia. Xenon is the rarest and the heaviest of the rare gases. It is present in the atmosphere in the ratio of 1 part in 20 million of air. The word "xenon" is derived from the Greek and means stranger. It was discovered by Ramsay and Travers in 1898 in the residual remaining after the evaporation of liquid air. It is inert and forms no stable compounds with other elements. Several unstable hydrates are possible (Xe_4H_2O) and the deuterite $Xe 6D_2O$.

PROPERTIES

The atomic and molecular weights are 131.3, the boiling point is $-107.1°C.$, melting point $-112°C.$, the density of the gas is 5.85 gm. per liter. The specific gravity of the liquid is 3.52 at $-109°C.$

The critical temperature is 14.8°C.; critical pressure 57 atmospheres. Xenon is slightly more viscous than air at room temperature.

USES

Cullen and Gross found xenon to possess anesthetic properties. Striking similarities exist between the solubility data for xenon and ethylene. The Bunsen absorption coefficient at 37° is 1.7 in oil and 0.085 in water for xenon. For ethylene the Bunsen coefficient is 1.3 in oil, 0.09 in water and an oil/water ratio of 14.4. The oil/water solubility is 20 at 37.5°C. A mixture of 80% xenon and 20% oxygen produces light surgical anesthesia within a few minutes. Anesthesia is of the same depth as that of ethylene. Recovery is rapid. The cost and scarcity of the gas *prohibits its use as a surgical anesthetic.* It, however, is a valuable pharmacological tool. The rate of uptake and distribution of anesthetics in tissues has been studied by Pittinger and Cullen by using Xenon (Xe 135) which has been made radioactive in a nuclear reactor. A bluish color results when Xenon is subjected to activation by an electrical current in a rarefied atmosphere.

KRYPTON

Krypton has been compared with xenon for anesthetic potency. Apparently it is ineffective, even though it has an oil/water ratio of 9.6, a Bunsen absorption coefficient of 0.43 for oil and for water of 0.045 at 37°C.

HYDROGEN

HISTORY

Hydrogen is the lightest element known. It is of interest in anesthesiology because it has been suggested as a diluting agent because it is light and is chem-

ically inert in vivo. It possesses no narcotic properties. Cavendish first recognized the gas as an element in 1776. It was later given the name hydrogen by Lavoisier.

ACTIVITY

Hydrogen is a colorless, odorless and tasteless gas which liquefies at —226°C. Two volumes dissolve in 100 volumes of water at 760 mm. Hg and 0°C. Hydrogen is extremely active chemically and *combines with many elements to form* hydrides. Ammonia is the hydride of nitrogen. Oxidation, or union with oxygen, occurs with explosive violence. Its use in anesthesia and inhalation therapy is objectionable on this account.

PROPERTIES

The atomic weight of hydrogen is 1.008; the molecular weight is 2.016, because the molecule is diatomic. The specific gravity is 0.069 (air $= 1$). One liter weighs 0.08987 grams. The viscosity at 20°C. is 88 micropoises (air 182). The lightness of the gas would render it more serviceable than helium which is twice as heavy. Hydrogen is interesting in that it possesses several *isotopes.* Approximately 1 in 5000 atoms possesses a mass of 2. This "heavy" *hydrogen is called* deuterium *and is represented by the* symbol D or H^2. A third isotope, tritium $—(H^3)$, occurs to the extent of 1 in every 1,000,000,000 atoms. The ordinary hydrogen atom (mass 1.008) is called *protium.*

PREPARATION

The commercial source of hydrogen is the electrolysis of the oxide or water. The oxide of deuterium, known as *"heavy water"* electrolyzes with more difficulty than ordinary water. This behavior is

utilized in the preparation of "heavy" hydrogen. Although it is possible that deuterium oxide possesses biological significance, its relationship to anesthesia is unimportant according to present day knowledge. Its only use is a tracer in determining distribution and elimination of drugs.

HYDROGEN IONS AND pH

The hydrogen nucleus (H) or proton, is important in the formation and structure of acids. Acids act as proton donators and may transfer protons to other substances capable of receiving them. When an acid forming substance, such as hydrogen chloride, dissolves in water, the proton transfers from the hydrogen to water to form oxonium ion (H_3O^+) and chloride ion (Cl'). The oxonium ion is positively charged. The remainder of the acid is negatively charged. The older concept proposed the formation of *hydrogen ion* as the cation (H^+) and the remainder of the molecule as an anion when an acid was dissolved in water. The term "hydrogen ion" is still retained

in physiologic and medical literature. The concentration of hydrogen ion, or, as it is often expressed, cH is an indication of the degree of acidity. Hydrogen ion is expressed for the sake of convenience, as *pH which is the reciprocal of the concentration expressed as the negative logarithm of base 10.* The concentrations of H^+ and OH^- in water or dilute aqueous solutions is a constant.

At 25°C. pure water or a neutral solution contains 1×10^{-7} moles of H^+ or OH' per liter (1/10,000,000 normal). The pH is expressed as 7. A normal solution of an acid if 100% ionization occurred would have a pH of 0. A 1/10 normal solution would have a pH of 1, a 1/100 normal a pH of 2, a 1/1000 normal a pH of 3, and so on up to pH 7.0. The pH scale is used to indicate degrees of alkalinity because a definite reciprocal relationship exists between hydroxyl ions and hydrogen ion. A normal solution of a completely ionized base has a pH of 14, a 1/10 normal a pH of 13, a 1/100 normal a pH of 12 and so on down to pH 7.0.

Gas Analysis

INTRODUCTION

THE QUALITATIVE and quantitative analysis of gases, as a rule, requires skill and experience. In many cases elaborate apparatus and tedious manipulations are necessary. Few clinicians have either the time or experience or even the occasion to do their own analyses. However, they should be familiar with the basic principles which underlie methods for analyzing gases they ordinarily use. The following discussion, therefore, will deal largely with generalities and basic concepts of gas analysis. Technical details not only would be of little interest to the clinician but also would comprise a treatise in themselves and are, therefore, not included.

GENERAL PRINCIPLES

Gases may be analyzed qualitatively and quantitatively by either *chemical* or *physical* methods. For many years the only methods of analysis were chemical. The advances in electronics have led to the development of physical methods. Both types of analyses have their place. Some gases are best analyzed by chemical methods; others by physical. Usually continuous analysis involves physical methods.

CHEMICAL METHODS OF ANALYSIS

In order to determine the percentage composition of a mixture of gases, whether it be by a physical or chemical method, one must know the temperature, pressure, and volume at the time of sampling. The sample is collected in glass tubes under mercury as a rule for chemical methods. In many physical methods the gases are drawn in a continuous stream into the apparatus. The requirements for sampling will be discussed in more detail as each method and gas is described.

Numerous chemical methods utilizing a variety of apparatus are used but they may be resolved into three fundamental basic types: (1) *Absorptiometric*, in which the temperature and pressure of the specimen remain constant and the changes in volume produced by absorbing the unknown gases with chemical reagents is measured; (2) *Manometric*, in which the temperature and volume of the specimen remain constant and the changes in pressure induced by absorption are measured; (3) *Conversion* methods, in which a measured volume of a gas reacts at known temperature and pressure with a suitable reagent to form an end product which may be determined volumetrically, gravimetrically, colorimetrically, or by special techniques.

ABSORPTIOMETRIC METHODS

Absorptiometric methods are widely employed. Many types of apparatus are

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available. Each varies widely in details of construction. However, the basic underlying principle is the same in all of them. Only the more important and those used in anesthesiology can be described here.

THE ORSAT APPARATUS

This is a commonly used type of analyzer which has been modified by many different workers to suit a particular need or project. Frequently the term Orsat is co-named with the name of the individual proposing the modification, as for example, Orsat-Henderson. Each modification has been devised for some particular purpose, but essentially all have the same features, fundamental parts and principles of operation.

The most important part of any quantitative gas analysis apparatus is the precision instrument used for measure-

ments. In the Orsat (Figs. 1.7, 2.7), this consists of a vertically placed burette calibrated in cubic centimeters or fractions thereof depending upon the precision required. This burette is of varying capacity, depending upon the purpose for which the apparatus is intended. Usually it is of the 100 ml. capacity. The zero point is at the top. The upper end is connected to a three-way stopcock, one part of which communicates with an inlet through which the sample to be analyzed is admitted. The other limb of the stopcock is connected with the absorption chamber or pipette. The lower end of the burette is connected, by means of a rubber tubing, to a leveling bulb. This consists of a reservoir containing a displacing fluid which may be raised and lowered. The leveling bulb has a capacity approximately two and one-half times that of the burette. When
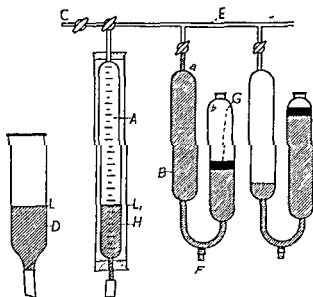
Fig. 1.7. Gas analysis apparatus which measures change of volume while temperature and pressure remain constant. The glass burette (A) is connected to the absorption pipette (B). The sample is drawn into the burette through the inlet (C) by raising and lowering the leveling bulb containing a displacement medium (D). The gas is forced into the absorption pipette by raising the leveling bulb. The reagent passes from (a) to (b) of the absorption pipette as the gas passes into it. Several pipettes may be connected to the manifold (E), each containing a different reagent in order that several gases may be absorbed from the same specimen. Pipette (B) shows arrangement of reagent before gas is introduced, (B₁) while gas is being absorbed. The stopper (F) is for emptying reagent from the

pipette. The surface of the reagent (G) may be covered with mineral oil to preserve it from evaporation and oxidation. Air jacket (H) serves to maintain a constant temperature. Both levels (L) and (L₁) must be equal when volumes are measured in order to have the pressure in apparatus equal to atmospheric. The Orsat and Haldane apparatus both employ the principles embodied here.

the leveling bulb is raised to the zero level of the burette, the fluid fills the burette and the gases contained within it are forced to the outside or into the absorption chamber, depending upon which way the stopcock is turned. The sample is drawn into the burette by lowering the leveling bulb towards the bottom of the burette, after having first filled it with the displacing fluid. Gases in the burette are adjusted to atmospheric pressure by having the meniscus in the burette and leveling bulb at the same level. Thus, by raising and lowering the leveling bulb gas may be drawn in and out of the burette. The displacing fluid must not react with or dissolve any of the gases to be analyzed. It must also have a low vapor pressure to be useful. Mercury possesses these qualities and is, undoubtedly, the most satisfactory displacing fluid. Aqueous solutions of various acids, bases or salts with which the gases being analyzed do not react and in which they are poorly soluble may be used instead of mercury. The burette is usually enclosed in a transparent jacket containing air or water which helps maintain a constant temperature.

Absorption chambers (also called pipettes) vary in construction. The usual type is composed of two transparent chambers, one placed slightly above the other, whose bottoms communicate by means of a U-tube. The top of the uppermost chamber is connected to one limb of the three-way stopcock of the burette. The gas is transferred to and absorbed in this portion of the pipette. The second chamber, which is open at the top, serves as a reservoir for the reagent displaced from the first portion of the sample. The pipette is filled with the specific reagent necessary for a par-
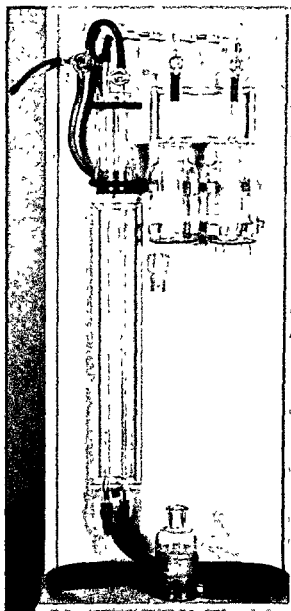
Fig. 2.7. Orsat-Henderson Gas Analyzer.

ticular gas present in the sample.

Absorption occurs primarily from the surface of the liquid. Therefore, the greater the surface of the reagent presented to the gas the more rapidly will the absorption proceed. The surface is usually increased by placing glass tubes or beads in the first chamber. These become moistened by the reagent. The sample of gas to be analyzed is drawn into the burette at room temperature

and adjusted to atmospheric pressure. It is then forced in and out of the absorption chamber by raising and lowering the leveling bulb until there is no more shrinkage in volume of the sample. When absorption is complete, the remaining unabsorbed gas is redrawn into the burette and its volume measured after adjustment to atmospheric pressure has been accomplished by the equalization of fluid levels in the bulb and burette.

A number of gases may be analyzed in succession from a simple sample by using different reagents. Several absorption chambers are filled with appropriate reagents. These are placed on a single manifold. A mixture of carbon dioxide, oxygen, cyclopropane and nitrogen, for example, may be analyzed by passing the sample into three successive chambers. The first, containing sodium hydroxide, removes the carbon dioxide; the second containing pyrogallic acid removes oxygen; the third containing fuming sulphuric acid removes cyclopropane. The residual gas is nitrogen.

The Haldane Apparatus

The Haldane gas analyzer is similar in principle to the Orsat. It allows greater precision than the Orsat. The Haldane gas analyzer is employed for physiological studies of respiratory gases because it permits accurate analyses of small samples. The Orsat is employed for commercial and industrial purposes. It may be used for absorbing hydrocarbons, carbon dioxide, carbon monoxide, oxygen and so forth. Volumes as small as 10 ml. of respiratory gases are analyzed using the Haldane. Each constituent may be determined to an accuracy of 0.01%. The burette is calibrated precisely to hundredths of a ml. It is surrounded by a water jacket, through which a stream of

compressed air may be passed to agitate the water so that constant and even temperatures are assured in the burette. The upper portion of the burette is connected to a gas sample inlet and two absorption chambers by means of a four-way stopcock. The lower end is connected to a leveling bulb. A non-calibrated burette of exactly the same diameter and capacity as the calibrated one is submerged in the water jacket to be used to determine the correction factor due to changes in volume from variations in temperature. The leveling bulb operates in the same manner as in the Orsat.

The Van Slyke Volumetric Apparatus

Gases dissolved in liquids or combined with constituents dissolved in fluids may be determined quantitatively on the Van Slyke volumetric apparatus (Fig. 3.7). This consists of a calibrated pipette attached to an extraction chamber and a leveling bulb containing mercury. The gases in the fluid to be analyzed are extracted in the chamber by means of appropriate reagents and their total volume is measured. Carbon dioxide and oxygen in blood, for example, are released by means of lactic acid and potassium ferricyanide. Changes in volume are then noted after the appropriate absorbing reagent is admitted into the chamber. Carbon dioxide is absorbed with sodium hydroxide; oxygen with sodium hydrosulphite. The shrinkage in volume is noted. A vacuum is created in the apparatus to extract the gases from the liquid by lowering the leveling bulb and withdrawing mercury from the chamber. Gases are adjusted to atmospheric pressure by use of the leveling bulb, as is done in the Orsat. Readings are taken at room temperature. The volumes may

then be recalculated to standard conditions. The volumetric Van Slyke is the type ordinarily found in general clinical use in hospitals for studies of carbon dioxide combining power.

SCHOLANDER MICROMETER ANALYZER

The Scholander micrometer gas analyzer permits the determination of carbon dioxide, oxygen and nitrogen in ½ ml. samples with an accuracy of .015 per cent. A gas sample is introduced into a reaction chamber connected to a micrometer burette which is balanced by means of an indicator drop in a capillary
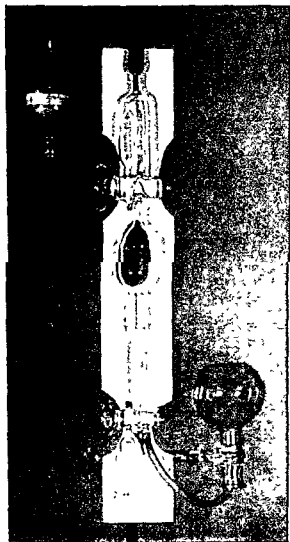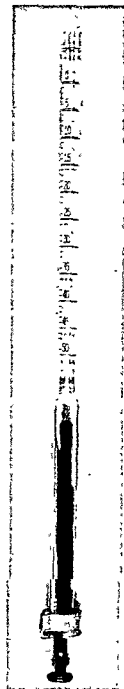
Fig. 4.7. Scholander microanalyzer pipette for blood gases.

Fig. 3.7. Volumetric apparatus of Van Slyke.

against a compensating chamber (Fig. 4.7). Absorbing fluids for the particular gas are tilted into the reaction chamber without causing any change in total liquid content in the system. During absorption of the gas mercury is delivered into the reaction chamber from the mi-
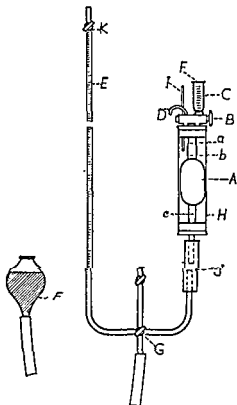
FIG. 5.7. The manometric type of gas analysis apparatus (Van Slyke and Neill) is shown. The burette (A) is equipped with a double stopcock (B) to which are attached measuring cup (C) and outlet tube (D) which are used to introduce or eject samples or reagents. This burette is connected to manometer (E) and a mercury leveling bulb and reservoir (F). The bulb can be closed off from the apparatus by the three-way stopcock (G). A water jacket (H) surrounds the burette to maintain a constant temperature which can be watched with thermometer (I). The burette is usually calibrated at 0.5 cc. (a), 2 cc. (b), and 50 cc. (c) marks. A vacuum can be created in the apparatus to extract gases from liquids by lowering the leveling bulb so that the level of mercury falls to the 50 cc. mark. The extracted gases are then compressed to 2 or 0.5 cc., and pressure noted on the manometer. A reagent is introduced in the cup (C) to absorb a particular gas. The volume is readjusted to 2 cc. or 0.5 cc., and the differences in pressure before and after absorption are used to compute the volume of gas absorbed. The flexible joint (J) allows a to and fro motion for shaking and mixing of reagents and extraction of gases. The stopcock (K) allows use of the manometer as either the closed or open type.

crometer burette so as to maintain balance of the gas against the compensating chamber.

MANOMETRIC METHODS

The second, or manometric group of methods of gas analysis is used to measure changes in pressure produced by chemical absorption of gases at a fixed temperature and volume. The best known apparatus employing this principle is that of Van Slyke and Neill (Figs. 5.7, 6.7). The manometric apparatus permits greater accuracy and precision than *the volumetric apparatus of Van Slyke*. Gases dissolved in liquids as well as mixed samples of gases may be determined quantitatively by this technique. The gas content of as small a sample as 1/10 ml. of fluid may be analyzed to an accuracy of 0.01%. The apparatus consists essentially of a manometer, a leveling bulb, and a burette. The burette which has a capacity of 50 ml., has three calibrations, one at the 50 ml. mark, one at the 2 ml. mark and the other at the ½ ml. mark. It is constructed in a bulb-like fashion. A double stopcock and a calibrated 6 ml. cup for admitting and ejecting liquids and gases from the apparatus are attached to the burette. The entire burette is enclosed in a permanent water jacket to maintain a constant temperature. The burette is connected to the manometer by a flexible joint so that it can easily be shaken by a motor or magnetic agitator to accelerate chemical reactions. A manometer of the closed type communicates with the leveling bulb and the burette may be isolated by means of a three-way stopcock. The leveling bulb, filled with mercury, may be elevated to expel liquids from the apparatus or be lowered to create a vacuum in the burette for extraction of gases. Gases are usually extracted from liquids at a 50 ml.

volume and are compressed to either the 2 ml. or ½ ml. volume depending upon the size of the sample and the nature of the liquid used. The total pressure of the liberated gases in millimeters of mercury is read on the manometer. After the proper reagent for a particular gas is admitted into the chamber and the gas is absorbed, the remaining gas is restored to the original 2 cc. volume. The difference in pressures before and after absorption is used to calculate the volume of the absorbed gases.

Computations

To facilitate tedious computations, Van Slyke and his coworkers have prepared a table of constants for certain gases at given temperatures with which the pressure changes in millimeters of mercury may be multiplied to determine the volume of the gas in a given volume of fluid. Blood may be analyzed for total content of carbon dioxide, oxygen, nitrogen, cyclopropane, ethylene and nitrous oxide.

Blood for gas analysis must be collected anerobically and not allowed to come in contact with air; otherwise, this would change both the oxygen and carbon dioxide content. Specimens are usually collected over mercury or under mineral oil. Mineral oil may not be satisfactory for use in anesthesia studies because anesthetic drugs are soluble in hydrocarbons and would be extracted from the blood.

The blood is mixed with a reagent containing saponin, which hemolyzes the cells; lactic acid which liberates carbon dioxide from the carbonates and the carbamino compound, and an oxidizing agent (potassium ferricyanide) which converts hemoglobin and oxyhemoglobin to methemoglobin to liberate oxygen.
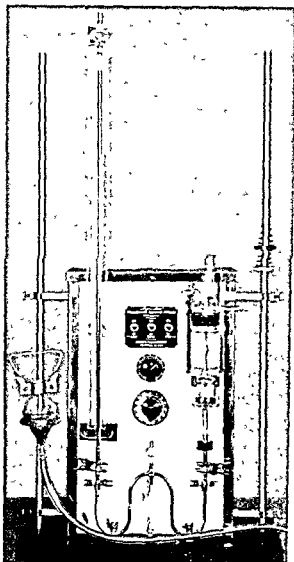
Fig. 6.7. Manometric apparatus of Van Slyke and Niell for analysis of gases in liquids.

Oxygen and carbon dioxide are absorbed by sodium hydroxide and sodium hydrosulphite. Nitrogen, cyclopropane, nitrous oxide or ethylene are determined as residual gases, since these are not absorbed by any particular reagent. Seevers and Orcutt have studied the analysis of these gases by this method and have prepared a table of constants from which the amount present is computed from the pressures of the residual gas. The oxygen and carbon dioxide are first absorbed and the remaining gas is assumed to be an anesthetic gas. Blood

containing ether cannot be analyzed satisfactorily by this technique because the ether possesses a high vapor pressure and dissolves in the reagents in different proportions and invalidates results. Shaw, Steel and Lamb have devised a method for removing the ether from the extraction mixture with a solution of equal parts of saturated sodium chloride and glycerine in a Hempel pipette and readmitting them again into the apparatus where the analysis is continued in the usual manner.

CONVERSION METHODS

The third type of analysis consists of a group of miscellaneous chemical reactions. For the want of a better designation the term "conversion methods" is used to describe this type. The gas is converted to a by-product, usually a non-volatile one, and the product is in turn quantitatively analyzed by some chemical or physical method. Each technique embodying this principle is individualized for a particular gas. Carbon dioxide, for example, may be passed into solutions of the hydroxides of the alkaline earth metals. These are precipitated as carbonates. The carbonates are then determined gravimetrically. One technique employed for the quantitative estimations of hydrocarbons, alcohols and ethers, such as ethylene, cyclopropane and ethyl or vinyl ether, is of particular interest to anesthetists. This utilizes the iodine pentoxide train (Fig. 7.7). A measured sample containing the gas or vapor of the drug at a known temperature and pressure is drawn through a tube 2.5 cms. in diameter and 25 cms. in length filled with asbestos impregnated with iodine pentoxide heated to 200-300°C. Organic substances are oxidized to carbon dioxide and water by the iodine pentoxide. In the process free iodine, hydrogen iodide, or both are liberated. The iodine and hydrogen iodide are collected in a potassium iodide solution and are determined quantitatively by titra-
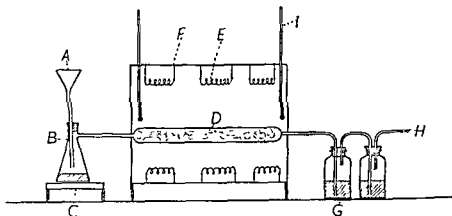
Fig. 7.7. Schematic representation of the iodine pentoxide train. The specimen of fluid containing the gas or volatile liquid is introduced through funnel (A) into receiver (B). Liquids are volatilized by heat from the electric plate (C) and drawn by suction through the tube (D) containing iodine pentoxide mixed with asbestos. The mixture is heated by the electric coils (E) of the oven (F). The iodine which is liberated is caught in the receiver (G) containing potassium iodide solution. The oven is thermostatically controlled. Suction is applied at (H).

tion with standardized sodium bisulphite or thiosulphate solutions. The carbon dioxide formed is not utilized. Another example of a conversion method for detecting and estimating a gas is the *analysis of carbon monoxide*. Carbon monoxide reacts with hemoglobin to form carbon monoxide hemoglobin which is *bright red and is easily estimated in a colorimeter.* Nitrous oxide also may be determined colorimetrically in a similar manner by use of the diazo reaction.

More detailed discussion of individual reactions for particular gases or vapors will be described further on in the discussion of individual agents.

METHODS OF DESIGNATION OF GAS CONCENTRATIONS

Quantities of gases in physiology and pharmacology are usually expressed in terms of *volumes per cent.* This term indicates that each 100 ml. of a gas or liquid contains, or may yield by an appropriate analytical method, so many ml. of the given gas at the temperature and pressure of the experiment. Thus, 50 volumes per cent oxygen means that a 100 ml. sample of liquid or gas contains a total of 50 ml. of combined and free oxygen. Gas quantities may also be expressed by weight, usually *in grams or* milligrams per liter or per 100 ml. In biochemical studies it is common to express the quantity of the gas in *moles* or fractions of a *mole per liter.* The term "volumes per cent" may be misleading when the *total* pressure of a mixture of gases is not at normal atmospheric pressure. The concentration of a gas in a mixture may be accurately expressed in terms of *tension* or pressure at a given temperature when there are deviations from normal atmospheric pressure (Chap. 3).

PHYSICAL AND INSTRUMENTAL METHODS OF GAS ANALYSIS

DIFFERENCES BETWEEN CHEMICAL AND PHYSICAL METHODS OF ANALYSIS

Chemical methods of analysis have a number of drawbacks which limit their usefulness. Some objectionable features are as follows: (1) Specific methods for analysis of certain gases are not available. For example, helium, nitrogen and nitrous oxide do not react with reagents to form specific compounds and are, therefore, not amenable to chemical analysis. (2) Large samples are often required for analysis because micro techniques are not available. (3) The sampling is individual and intermittent. Continuous analysis is not always possible. (4) The method of analysis is often slow, tedious and cumbersome. (5) Often, particularly in clinical studies, it is desirable and necessary to perform the analysis at the scene of the experiment. Most chemical methods do not permit this.

These inadequacies of chemical methods have prompted the development and perfection of physical methods of gas analysis. Many devices embody physical principles as the basis for the analytical technique and permit rapid, continuous analysis of a single gas and, in certain cases, simultaneous analysis of the components of a mixture of several gases. Many of these devices require microsampling, are automatic and provide a permanent record. Many permit the detection of momentary changes in concentration which are often overlooked when chemical methods are employed.

Much of this type of apparatus, once it is calibrated and placed in operation, is capable of continuous performance.

DISADVANTAGES

There are, however, disadvantages to physical methods also. Some of these are as follows: (1) The apparatus is cumbersome and difficult to operate in some cases. In many instances, the apparatus is the assembly of a complex mechanical or electrical device. (2) The cost of the device is often prohibitive because of its complexities. (3) Many devices are not standard pieces of equipment and are not available commercially. Often they must be custom built. (4) The mechanisms are often delicate. They easily become deranged and develop flaws. Expert mechanics and technicians are required to service them. (5) It is possible for the apparatus to become deranged and still appear to be functioning properly. It may therefore record erroneous quantities, unbeknownst to the operator. (6) In many cases standardization of the apparatus by chemical methods is necessary. The calibrations are often tedious and time consuming.

SPECIFIC AND NON-SPECIFIC PHYSICAL METHODS OF ANALYSIS

Physical methods of analysis are of two types—specific and non-specific. In *non-specific methods* a physical property common to a class of substances, such as the ability to conduct heat or sound, the diffusibility, the index of refraction or the viscosity is determined. In *specific methods* some unique property peculiar to one gas which is not possessed by the other gases in a mixture of several gases is used as the basis of analysis. For example, oxygen is paramagnetic. This property is not possessed by gases, such as nitrogen, helium or carbon dioxide, which are ordinarily used in conjunction with oxygen in anesthetic techniques. In the following paragraphs some of the important physical properties of gaseous compounds and how they are utilized for gas analysis are discussed.

NON-SPECIFIC METHODS

METHODS BASED ON THERMAL CONDUCTIVITY OF A GAS

Apparatus relying upon thermal conductivity of a gas as the basis for analysis is suitable for the quantitative determination of certain gases. Each gas conducts heat at a different rate, depending on its molecular configuration. The passage of an electrical current through a wire of a moderate resistance causes heating of the wire. Two wires of identical resistance surrounded by identical media transmitting the same quantity of electricity will attain identical temperatures. Varying the composition of the medium surrounding a wire causes a variation in the rate of conduction of heat in a wire. If heat conduction is retarded the temperature rises; if heat conduction is increased the temperature falls. Resistance to the passage of electricity increases if the temperature of a conductor rises and decreases if it falls. Analyzers embodying this principle are called *katharometers*. In such an analyzer one wire is surrounded by air or other reference gas and the other by the specimen of gas to be analyzed. The heat loss from the wire surrounded by the reference gas remains constant; that

om the wire surrounded by the unknown gas varies with the composition f the gas. The changes in resistance, neasurable by ohmeters, using the Wheatstone Bridge principle, are proortional to the quantity of unknown as present. Apparatus of this sort must e calibrated emperically with a known nixture of gases. Gross errors are introluced in analysis of respiratory gases lue to the presence of carbon dioxide. Obviously, apparatus of this design is mpractical for clinical anesthesia if lammable gases and vapors are being ised.

SONIC METHODS

The velocity of sound varies with the physical characteristics of the medium hrough which sound waves are propaated. Dublin, Boothby and Brown apolied this principle to analysis of mixures of oxygen and helium in inhalation herapy studies. Faulconer has advocated the use of apparatus based upon this principle for investigative studies in nesthesia. The speeds of sound of common gases and vapors at 25°C. are as follows: nitrogen 338 meters per second, air 332 meters per second, oxygen 317 meters per second, nitrous oxide 362 meters per second, carbon dioxide 258 meters per second, ether vapor 179 meters per second, and water vapor 405 meters per second. In order to use apparatus based on this principle the identity of each of the gases in the mixture to be analyzed must be known. This technique of analysis is not suitable unless the velocity of sound of each component of the mixture to be analyzed is propagated at a significantly different rate from the other. If more than two gases are present in a mixture, the one propagating sound at the slowest velocity must

be selectively absorbed before the mixture can be analyzed on the apparatus. Faulconer and his associates have analyzed mixtures containing ether, nitrous oxide, carbon dioxide and oxygen by using the sonic technique in combination with other techniques. The ether is first removed by absorption by sulphuric acid after which oxygen determinations are made using the Pauling principle (para magnetic qualities). The carbon dioxide is then absorbed and nitrous oxide is then analyzed using the sonic method.

TYPES OF ANALYZERS

There are several types of analyzers embodying this principle. Some use oscillators as the source of the sound. Sound waves are supplied at a constant frequency. The sound waves enter one end of a smooth walled tube, whose length can be varied. The tube is filled with the gas and its length is varied until resonance occurs. The tube length corresponds to the wave length of the sound being transmitted through the gas. The quantity of gas is then computed from this reading from previously calibrated curves obtained from known mixtures of gases. In other analyzers, an electronic oscillator at one end of a smooth walled tube of fixed length sends sound waves into the tube. A sensitive microphone at the other end detects the magnitude of the sinal variations and amplitude of the sound waves. After amplification, the variations are indicated on sensitive micro-voltmeters. The readings of the latter are translated into terms of percent composition from calibrations previously made on known mixtures of gases.

VISCOSIMETRIC METHODS

Viscosimetric methods are employed

for detection and quantitative estimation of gases whose chemical and physical properties do not lend themselves to other methods of analysis. Viscosimetric methods are generally used for analysis of mixtures containing high molecular weight gases, such as hydrocarbons, or inert gases which have relatively low or high viscosities compared to those of other gases of similar density. The viscosity of a gas may be determined by measuring its resistance to flow through a capillary tube or a viscosity pipette. The gas is forced through the capillary tube under a constant pressure. This is accomplished by allowing a column of mercury to fall through a glass tube connected to the gas sampling bottle. As it does so, it drives the gas from the sampling bottle through the capillary tube. The time required for the column of mercury to pass a given distance, marked off by two points on the glass tube, is determined for the unknown gas and is compared with the time required for it to fall the same distance when air or other reference gas of known viscosity is used. Other methods of determining viscosity are also available but they are not adaptable for gases used in anesthesiology.

IDENTIFICATION BY DETERMIN-ING THE RATE OF EXPANSION

The rate of passage of a gas from an orifice of extremely fine bore is measured and compared to the rate of effusion of a reference gas under identical temperature and pressure. The number of molecules of a particular gas passing through the orifice depends upon the velocity only since the number of molecules of the gas in the container are the same, irrespective of the nature of the gas as long as temperature and pressure are

constant. The time of efflux depends upon the velocity, which in turn is related to the density in accordance with Graham's Law. The density is inversely proportional to the square root of the time required for a given amount of gas to effuse through the orifice. Instruments employing this technique are called *effusiometers*. Unless the orifice is minute and its diameter much less than the mean free path of the gas, results are variable and inaccurate. The mean free path of the gas molecules should be approximately 10 times the orificial diameter.

IDENTIFICATION BY DETERMINA-TION OF DENSITY

Density, as has been mentioned previously, is the mass of a unit volume of a gas at a specific temperature and pressure. Usually, density is expressed in terms of grams per liter at standard conditions. Specific gravity, on the other hand, is the ratio of a mass of a unit volume of a substance to the mass of an identical volume of a reference substance. Usually water is the reference substance in the case of solids and liquids, and air in the case of gases (at standard conditions or other identical conditions). In identifying a gas by its density, as in the determination of specific gravity, a comparison is made between the density of the gas and that of a known volume of air. Therefore, methods involving the measurement of density are actually measurements of specific gravity rather than absolute density. Determinations of absolute density are applicable for identification of individual pure gases. In determinations of density a given volume of the gas is weighed directly (method of Regnault). The indirect method (Victor Meyer) may

also be used. In the latter method a volume of a liquid is first weighed and allowed to vaporize after which the volume of its vapor is measured. When binary gas mixtures are to be analyzed specific gravity is (first) determined. When specific gravity is determined a special balance called a specific gravity balance is employed. By use of the balance the buoyant effect of a gas upon a body immersed in it is compared with that of a reference gas (air).

INDEX OF REFRACTION

The speed of light is decreased as light passes from a lighter, less dense medium to a heavier one. Also, as the rays of light enter the denser medium they are bent towards the norm. This bending of the rays is called *refraction*. The ratio of the speed of light in a vacuum to that in a particular medium is known as the index of refraction of light for that medium. The index of refraction is proportional to the degree of bending. The degree of bending may be determined with an instrument known as a *refractometer*. The refractive index of light passing through a vacuum at 25°C. is unity (1.000). For water at 25°C. it is 1.320. Commercial refractometers measure indices between the range of 1.300 to 1.38400. These are suitable for liquids and solids. The refractive indices of most gases are numerically so close to each other, and to that of air, that the techniques of refractometry ordinarily used for solids and liquids are unsuitable.

INTERFEROMETRY

The technique of *interferometry* is better adapted for determining refractive indices of gases. Interferometry is based upon the following physical behavior of light. When two sets of light waves ar-

rive at a given point simultaneously, they may reinforce each other, in which case the light appears brighter. If the waves of light could be visualized as being crests and troughs, the crests would meet crests and troughs meet troughs. However, if they arrive "out of step," that is, a crest meets a trough, they nullify each other and produce darkness. A dark band, therefore, results at the point of meeting. This cancelling of beams of light waves is called *interference*. Interference is caused by bending of the beams of light as they traverse a medium. The degree of interference is measured by an instrument known as an *interferometer*. Since the interference depends on bending of light waves as they traverse a medium and varies with the degree of bending, the interferometer can be used to measure the index of refraction. The basic operation of an interferometer is as follows (Fig. 8.7): A beam of light is divided into two beams by a lens or parallel slits in a diaphragm. One beam passes through a tube which contains the reference gas, usually air, while
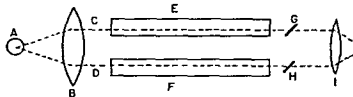
FIG. 8.7. Schematic representation of interferometer. Light from mercury vapor lamp (A) passes through concave lens (B) which parallelizes rays into 2 beams which pass through slits (C) and (D) and through tube (E) containing sample of unknown gas and tube (F) containing reference gas. Rays pass through matched glass plates (G) and (H) placed at 45° angle to beams. Plate (H) is fixed while (G) is attached to micrometer lever which can be rotated. The amount of rotation is indicated by the micrometer. The magnifier (I) is used to view the interference bands caused by passage through the gases. The rotating plate serves to position the central band of the series of interference bands.

the other passes into a second tube which contains the unknown gas. The two beams are recombined by a lens after traversing each tube and as they emerge at the exit end of each tube. The beams each pass through two matched glass plates. One plate is at a fixed position of 45°; the other may be rotated by a micrometer rotating lever. The degree of rotation of the movable plate is indicated on the micrometer. Rotation increases or decreases the effective optical path of one beam depending upon the direction. The plates thus are used to position the central band of the interference fringes. The interference fringes are formed at a microscope eyepiece at the exit end of the tube. The displacement of a set of fringes is a function of the differences in refractive indices of the gases in the two tubes.

Interferometers for gas analysis may be used in either one of two ways, (1) as a direct reading instrument using a calibrated curve constructed from mixtures of gases or (2) by comparing the index of refraction of the unknown with indices of refraction of two known mixtures of gases. In the latter method, two known mixtures of gases whose composition approximates that of the unknown, are used. One of these has an index of refraction above and one below the unknown. By interpolation, the unknown can be computed. When nitrogen-oxygen mixtures are analyzed carbon dioxide and water vapor must be absorbed because they introduce errors of great magnitude. The temperature and the pressure also must be maintained constant otherwise errors are introduced.

CALORIMETRIC METHODS

A gas which is completely and easily oxidized may be estimated quantitatively by measuring the heat output resulting from the oxidation. Oxidation is carried out in a combustion chamber with the aid of catalysts. The quantity of heat released is measured with thermocouples or by recording the changes in resistance of an electric wire. This method has little application in anesthesia due to its complexity.

SPECIFIC METHODS

METHOD UTILIZING MAGNETIC SUSCEPTIBILITY

The ability to become magnetized is a universal property of a substance somewhat akin to the ability of a substance to become electrified. Substances capable of becoming magnetized do so when placed in contact with a magnet or are brought into a magnetic field. This may be demonstrated by suspending a rod shaped piece of a solid substance or an elongated tube containing a fluid in the gap between the north and south pole of a magnet. The rod or tube is introduced in the field at an angle of 45° to the magnetic lines of force. These lines of force, referred to as flux lines, are horizontal from one pole to the other. Substances such as iron, nickel and cobalt rotate from the 45° position and orient themselves horizontally between the poles of the magnet (Fig. 9.7). The longitudinal axis of a rod of the substance comes to rest parallel to the flux lines. Other substances, for example, aluminum, copper or chlorine are also oriented in the magnetic field and tend to rotate in the same way but to a lesser extent than iron. The torque, that is, the force which tends to rotate the rod from 45° to the horizontal position is less with these substances. The position
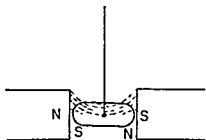
Fig. 9.7. A ferromagnetic substance orients itself parallel to the flux lines and concentrates flux lines.

Fig. 10.7. A paramagnetic substance tends to assume a position paralleled to the flux lines and tends to concentrate the flux lines.

they assume is not quite horizontal (Fig. 10.7). Still other substances show no rotation or tend to orient themselves away from the flux lines and affix themselves at right angles to the lines of force (Fig. 11.7). Substances which, when placed at an angle in a field, attempt to assume a position *parallel* to the flux lines are referred to as *paramagnetic*. They orient themselves in the magnetic field and exhibit a torque. Iron, nickel and cobalt, since they are so strongly magnetic, are sometimes referred to as *ferromagnetic*. Substances which are repelled out of a magnetic field and tend to orient themselves at right angles to the flux lines are called *diamagnetic*. Para and ferromagnetic substances are attracted towards the north pole of a magnet. A rod or a tube containing a diamagnetic substance is repelled from the north pole and orients itself at right angles at the weakest portion of an inhomogenous magnetic field. A paramagnetic substance tends to concentrate the flux lines while a diamagnetic one tends to disburse them and spread them apart (Fig. 12.7).

Diamagnetic and Paramagnetic Properties

A possible explanation of this behavior is as follows: Certain molecules are electrically neutral. Others are polar and have a positive charge at one end and negative one at the other, even though they appear to be electrically neutral. These are *polar molecules* or *dipole molecules* (Chap. I). These molecules, when placed in an electrical field, tend to orient themselves so that the positive end is at the negative plate and vice-versa. This tendency towards orientation in an electrical field and exhibition of a torque is called the *dipole moment*. The movement of electrons in an atom in a closed orbit produces a magnetic dipole of small moment. This is a permanent dipole. Placing such an atom in a magnetic field causes an induced magnetic dipole of a sign opposite to the permanent one caused by the electronic activity. Thus, an atom in a magnetic field has two magnetic dipoles, a permanent one and an induced one. The resulting or net dipole of these two is the permanent dipole minus the induced dipole. The pairing of electrons by covalent bonding nullifies the permanent dipole of a molecule. Thus, when such an atom is placed in a magnetic field only a negative induced moment is present. Substances
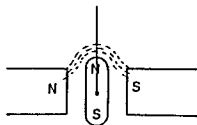
Fig. 11.7. A diamagnetic substance tends to orient itself at right angles to the flux lines and tends to spread them apart.
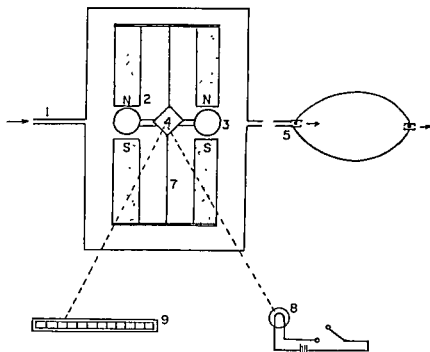
Fig. 12.7. Schematic representation of oxygen analyzer (Beckman) based upon the paramagnetic principle. (1) Inlet through which sample is drawn into chamber containing magnet (2) by squeezing bulb (5). Nitrogen filled test body (3) with mirror (4) is suspended between the poles of the magnet by a quartz string (7). Light from bulb (8) is reflected to scale (9).

which behave thus are diamagnetic. They are attracted towards the weakest part of an inhomogenous magnetic field. Certain substances which contain an odd number of electrons have a permanent magnetic moment which far exceeds the induced moment. They are the paramagnetic substances. They are attracted towards the strongest part of an inhomogenous magnetic field.

BECKMAN OXYGEN ANALYZER EMPLOYING THE PAULING PRINCIPLE

Principle

Oxygen has strong paramagnetic susceptibility. The other gases encountered in anesthesiology are all slightly diamagnetic. This property of oxygen is utilized for determining its concentration in mixtures of gases. The principle which utilizes the paramagnetic suscep-

TABLE 17

RELATIVE MAGNETIC SUSCEPTIBILITIES OF
COMMON GASES

Oxygen	100 0
Nitric Oxide	45 0
Nitrogen Dioxide	4 0
Hydrogen	0 123
Helium	0 057
Nitrogen	0 36
Carbon Dioxide	0 63
Ethylene	0.36

tibility of oxygen for analysis is known as the *Pauling principle*. It was first used in gas analysis by Linus Pauling of the California Institute of Technology in 1940. Gas analyzers are now available which utilize this principle. One of these, known as the Beckman Oxygen Analyzer, is widely used for both clinical and laboratory determinations of oxygen tensions. The instrument is constructed and operates as follows: A gas sample suspected of containing oxygen is drawn into a chamber containing a

small permanent magnet which produces an inhomogenous field (Figs. 12.7; 13.7). Between the poles of this magnet is mounted a dumbbell shaped receptacle which acts as a test body. This dumbbell shaped test body, filled with nitrogen, an inert diamagnetic gas, is held in position by a taut, fused silica fiber. A mirror is mounted on the test body. The magnetic field in which the test body is placed must be strong and non-homogenous. The test body is arranged so that it can turn in a horizontal direction in and out of the magnetic field. The amount of tortion depends upon the degree of magnetic susceptibility of the oxygen in the sample. The sample is drawn into a chamber containing the test body and the magnet. The sample is between the poles of the magnet and thus surrounds the test body. The degree to which the sample influences the existing magnetic field determines the amount of torsion. The degree of rotation of the test body, then, is in proportion to the magnetic substance in the sample. A beam of light from a flashlight bulb is cast upon the mirror on the test body and reflected to a scale which is calibrated in units of oxygen tension (mm. Hg) or in volumes per cent. A sample of gas may be analyzed almost immediately because equilibrium is attained within several seconds. A light weight portable model (Model D) is available for bedside use. The limit of error in this model is less than 2% and not clinically significant. More elaborate models are available for the precise determinations necessary for investigative work.

Technique

The gas is drawn from the sampling tube into the analyzing chamber by an aspirator bulb. A check valve at each end of the bulb assures a unidirectional flow. Thus, each compression of the bulb draws the analyzed specimen out of the chamber and ejects it to the outside air and replaces it with a fresh one. The sampling tube is placed directly into an oxygen tent or connected, by means of an adaptor, to a needle which is introduced into the mask or breathing tube or is attached to the outlet of a gas sampling receptacle. The gas must be dried. This is done by drawing it over silica gel before it passes into the analytical chamber. The silica gel is stained with a blue indicator. After repeated use the gel becomes exhausted by hydration. It can be used again if heated to 300°F. to drive off the water. It is blue when anhydrous and active, and pink when hydrated and no longer capable of absorbing water. A light switch is provided on top of the apparatus for illumination of the mirror (Fig. 13.7).

The instrument is delicate and subject to damage unless it is handled with care. The suspension (quartz string) for the test body is easily broken. This method of oxygen analysis is suitable only when other paramagnetic gases are absent. Nitric oxide, nitrogen dioxide and chlorine dioxide are other gases which manifest strong paramagnetic properties (Table 1.7). However, it is more than unlikely that these gases will be encountered in anesthetic gas mixtures. This type apparatus is used in anesthesiology and inhalation therapy.

Accuracy

Two sets of calibrations appear on the scale of the clinical model. One scale expresses the oxygen concentration in volumes percent at normal atmospheric pressure and room temperature (75°F.). Corrections must be made for variations in barometric pressure. The other scale

indicates the partial pressure of the oxygen. The calibrations in terms of partial pressure may be read directly and require no corrections for variations in barometric pressure. Corrections must be made for temperature. In precise determinations the instrument must be calibrated for the temperature at which the specimens are analyzed. The instrument (Model D) used for clinical purposes is calibrated to read at 75°F. but measurements may be made from 65° to 85° with less than 2% error.

METHODS OF EMPLOYING ABSORPTION OF RADIANT ENERGY

Types of Radiant Energy

INFRA-RED ABSORPTION

Molecules possess three kinds of energy: (1) *electronic energy,* (2) *vibrational energy* and (3) *rotational energy.* Mention of the first type—electronic energy— has been made heretofore (Chap. I). This type is due to the grouping of negatively charged electrons in orbits (energy levels) around the positively charged atomic nucleus. Atomic nuclei are constantly vibrating about their equilibrium positions with a definite frequency of vibration. The exact mode and their frequency are determined by the type and arrangement of the atoms composing the molecule. An analogy may be drawn between this vibration and the vibration of a spring supported body. The spring supported mass vibrates at a frequency which is a function of the weight of the mass and the strength of the spring. In the atom, as long as the electrons remain in a given orbit or energy level, the electron energy of that particular atom is stable. When one or more electrons moves to a higher energy level it does so with the absorption of energy in the form of heat, light or elec-

FIG. 13.7. Beckman oxygen analyzer designed for bedside use.

tricity. If one or more electrons move to a lower energy level, the atom then emits energy of one form or another. The energy necessary to cause a shift of electrons from a lower to a higher energy level is greater than that necessary to increase the vibrational energy of a molecule. The latter in turn is greater than the energy required to increase the rotational energy of a molecule. Radiant energy may be absorbed to effect these changes.

Radiant energy is emitted from its source in the form of electro-magnetic waves. Electro-magnetic waves vary in length from the extremely short, or cosmic rays, which have very high frequency and high energy, to the very long radio broadcast and ultrasonic waves which have low frequency and low energy. In between these extremes of length are the x-rays, various types of visible light and heat waves. The absorption of energy by molecules in the ultraviolet and in invisible regions of the spectra, in other words at the high energy regions, is associated with shifting of electrons to the higher energy level. Absorption of the longer wave lengths in the lower energy portion of the spectrum, such as the infra-red portion, is associated with increases in vibrational and rotational energies of the absorbing molecules. There is also a difference in behavior at the extremes of the infra-red spectrum. At the upper end of the infra-red spectrum, absorption of energy is associated with vibrational energy while the absorption of infra-red waves of the lower portion of the spectrum, where the longer wave lengths are located, is associated with increases in the rotational energy of the molecule.

The qualitative and quantitative analysis of numerous substances may be accomplished by measuring the degree of absorption of radiant energy. Solids, gases and liquids may be detected and determined qualitatively and quantitatively by utilizing this principle. Methods of analysis based upon this principle require the use of instruments known as *photometers* or *spectrophotometers*.

PHOTOMETERS AND SPECTROPHOTOMETERS

Photometers and spectrophotometers are instruments for detecting and measuring quantities of radiant energy. A photometer differs from a spectrophotometer in that the latter is selective. In a photometer the gas or other agent is exposed to the entire energy spectrum emitted by the source of radiant energy and the absorption of various wave lengths of light is determined. In the spectrophotometer the gas sample is exposed to certain pre-selected *fixed wave lengths* of radiant energy. These wave lengths are provided from a monochromatic source of energy. The source of energy emits light of a single wave length. A source of energy may be used which emits a mixture of rays of different wave lengths. These are passed through a filter which screens out all the wave lengths of radiant energy except the desired one.

SPECTROPHOTOMETRIC METHODS OF GAS ANALYSIS

Few gases absorb *visible* radiation in a manner which is adequate to make this method practical for gas analysis. For those that do a spectrophotometric gas analyzer may be used. A spectrophotometric gas analyzer consists of the following basic parts: (1) a source of energy which yields radiant energy of a single selected wave length, (2) an absorption cell which holds the gas, (3) a

detector which absorbs the energy not absorbed by the gas, and (4) an instrument for amplifying and recording the variations in energy passing through the cell to the detector.

Use of Non-Visible Radiation

Most gas analyzers rely either upon absorption of non-visible, infra-red or ultra-violet radiation as the basis of analysis. Ultra-violet absorption has limited value because it is a comparatively non-specific characteristic of individual molecules. Instead, it is a trait common to a multitude of gases. The absorption of infra-red rays, on the other hand, is a specific characteristic of certain molecules. The position and intensity of the infra-red absorption bands is a characteristic one for a particular compound and serves to identify the compound. Polyatomic molecules, such as those of carbon dioxide, water, carbon monoxide, nitrous oxide, ethylene, ether, cyclopropane and so on may be determined quantitatively by infra-red absorption. The method is not applicable for detection of gases having monatomic molecules, such as the rare gases or the diatomic elemental gases, such as oxygen or nitrogen.

Infra-red Ray Gas Analyzer

As in the case of the spectrophotometer, the infra-red ray analyzer is composed of (1) a source of radiation, (2) an absorption cell, (3) a detector, and (4) an instrument for amplifying the energy which has passed through the gas. Infra-red gas analyzers are usually of two basic types—the *dispersion* and the *non-dispersion* type. In the dispersion method all the radiation from an infra-red source is passed into a prism which disperses it into a spectrum of its component wave lengths. Radiation of a desired wave length is selected to the exclusion of other wave lengths and passed through the gas, into the absorption cell and to the energy detector. In instruments employing the non-dispersion principle the complete spectrum, that is, all the radiant energy emitted from the source, is passed through the cell containing the sample of gas to be analyzed. No particular wave length is selected.

Detectors

The detectors used in the infra-red ray analyzers are, likewise, of two broad types, the *selective* which respond only to infra-red rays of a given wave length, and the *non-selective* which respond to infra-red radiation of many wave lengths. Most detectors in infra-red absorbers operate on the "heat absorption" principle. The infra-red rays which are not absorbed by the unknown gas during passage through the absorption cell pass into and are converted to heat in the detector. The heat which is liberated may be measured by using a thermocouple, a thermopile, a bolometer or a gas thermometer. Thermocouples record the temperature which develops. In the thermopile a current is produced when the infra-red rays strike the junction of two dissimilar metals. The temperature is raised to a slightly higher level than the standard. Thermopiles operate in a vacuum. In the thermister (bolometer) the temperature of a wire in the detector becomes elevated by the heat, causing a change in resistance and variation in passage of an electric current. The gas thermometer consists of a small bulb containing a gas upon which the radiation falls. The heat formed causes the gas in the bulb to expand. This moves a flexible portion of the thermometer which serves as a mirror in an optical

system between a light source and a photocell, or as a half condenser whose electrical capacity varies with the changes in position. The first three types are termed non-selective detectors since they react to infra-red radiation of any wave length. The gas thermometer is selective because it reacts only to the radiant energy of specific wave lengths which are absorbed by the gas in the detector. The bulb in the thermometer is made specific for a given wave length of radiation by filling it with a gas of specific composition which absorbs the desired wave length of infra-red radiations and heats the gas which expands and in turn operates an optical detecting system.

The Liston-Becker Gas Analyzer

The Liston-Becker infra-red gas analyzer has been employed in recent years in clinical anesthesia to analyze carbon dioxide. This device employs the nondispersion selective detector principle. Infra-red rays are emitted by two electrically heated nichrome light sources (Fig. 14.7). A rotating blade synchronously interrupts the infra-red beams. One beam is directed into the reference cell which contains the reference gas and then into a detector. The other beam is passed through the sample cell containing the unknown gas and then into the detector cell. Both the reference gas and the detector cell are equipped with quartz windows to assure uninterrupted transmission and minimal absorption of the infra-red bands. Both the reference cell and the detector cells are filled with carbon dioxide. These cells are side by side separated by a diaphragm of a differential capacitance manometer. Gas in the sample cell absorbs some of this radiation and decreases the infra-red radia-
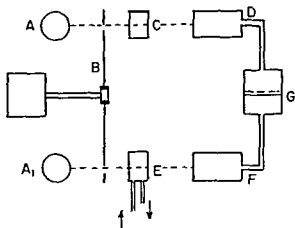
Fig. 14.7. Gas analyzer utilizing principle of infra-red ray absorption. Two nichrome light sources (A & A_1) emit infra-red rays into reference cell (D) through dummy cell (C). A_1 emits rays through sample cell (E) into detector cell (F). The reference cell and the detector cell are filled with the gas being analyzed (CO_2) but are separated by diaphragm of differential capacitance manometer. Pressure difference between reference cell and detector cell is adjusted by shutter in path of detector cell. The gas to be analyzed in sample cell (E) reduces infra-red rays passing into detector, thus decreasing the energy which reduces the pressure which is detected by the capacitance manometer which is translated in terms of per cent of gas by varying voltage.

tion reaching the detector. Less heat is produced in the detector cell than in the detector of the reference cell. Less pressure is then applied by the diaphragm in the capacitance manometer. The electrical capacity, therefore, varies with the increases and decreases in pressure in the detector cell. This causes a variation in electrical current which passes through the microvoltometer which is calibrated in terms of quantity of gas. The apparatus must be calibrated using carbon dioxide-oxygen mixtures of known composition analyzed by some other method, usually a chemical one.

ULTRA-VIOLET RAY ABSORPTION

The ultra-violet gas analyzer uses a mercury vapor lamp as a source of radia-

tion. The gas is introduced into an absorption cell through which the beam of radiant energy is passing. The radiation not absorbed by the gas in the cell passes into a photoelectric cell which acts as a detector. The cell is arranged so that a certain voltage is passing through it. This voltage increases or decreases as the amount of radiation reaching the detector element increases or decreases. The voltage is balanced with that of a Wheatstone bridge. Fluctuations due to absorption of ultra-violet light by the gas cause an imbalance which is read off on a microvoltometer and translated into terms of quantity of gas from calibrations. Ozone, acetone vapors, bromine, phosgene, sulphur dioxide and so on absorb ultra-violet light and may be analyzed by this technique. Nitrogen, oxygen, water vapor, ethyl ether vapor and trichlorethylene do not. Therefore, this method cannot be used for detecting and estimating these gases quantitatively.

Methods Using Visual Radiation

It has been mentioned previously that the methods based upon absorption of visual radiation by photometers and colorimeters are of limited value for gas analysis because few gases and vapors are able to absorb visual radiant energy in detectable amounts. These methods, however, are applicable for the detection and quantitative determination of solids and liquids. The methods, therefore, may be adapted for gases which are convertible to non-gaseous compounds that are detectable by colorimetric methods. For example, carbon monoxide may combine with hemoglobin to form carbon monoxide hemoglobin. This compound is bright pink and can be determined quantitatively in a photoelectric colorimeter. Oxyhemoglo-

bin may be distinguished from reduced hemoglobin by determining the amount of light transmitted through it (page 192).

Methods Based upon the Emission of Radiation by Gases

Some gases can be made to emit radiation, in which case the amount of radiation can be measured. If an electric current at high potential difference passes from one electrode to another through a gas interposed between these electrodes, the molecules of the gas emit radiation in the form of a spark, an arc or a glow discharge. The wave length of the radiation emitted varies with the substance exposed to the electrical energy. Each substance yields its own specific color, the intensity of which depends upon the concentration of the gas. Nitrogen may be analyzed by this technique by using an instrument known as the *nitrogen meter*. This nitrogen meter was devised by Lilly for use in physiologic studies. The sample of gas to be analyzed is drawn continuously through an electrical discharge tube by a pump so that one cubic millimeter passes through the analyzing tube per second at a low pressure not exceeding 2 millimeters of mercury. The gas glows as it is exposed to the high potential applied to the electrodes. Air glows with a bright pink color, oxygen a faint green, nitrogen a bright, orange pink, carbon dioxide a dim blue and water vapor a bright red. The light passes to a detector consisting of a photoelectric cell. A filter interposed between the flow discharging tube containing the sample and the detector permits exclusion of all of the light except that emitted by the particular gas which is being analyzed. The photoelectric cell is connected to an amplifier which operates an oscillating galvonometer and

yields a visual record which can be photographed.

METHODS DEPENDING ON ADSORBABILITY

Gas Chromatography

PRINCIPLE

Chromatography is a method of analysis which has recently been applied to gases. The term "chromatography" actually means to write with colors. However, this technique has nothing to do with colored compounds. Gas chromatography is also known as vapor fractometry, gas partition chromatography and vapor phase chromatography.

The basic principle in gas chromatography revolves about the ability of adsorbents, such as silica gel or activated carbon, to selectively retard the movement of several gases in a mixture along a tube. The adsorbent is packed into a tube, known as a column, several or more feet in length. The length of the tube is determined by the nature of the adsorbent. A non-adsorbable gas, referred to as carrier gas (also known as the eluent) under a nominal pressure, is passed through the column. Usually helium is employed. The mixture of gas to be analyzed is introduced through a valve at some point proximal to the entrance of the carrier gas into the column. A mixture of any number of gases which are acted upon by the adsorbent may be analyzed. The composition of the column may be varied according to the types of compounds under study. The adsorbent influences the movement of components of the sample so that each component moves along in the column at a different rate of speed. The mixture of carrier gases and sample passes from the column into a detector where the
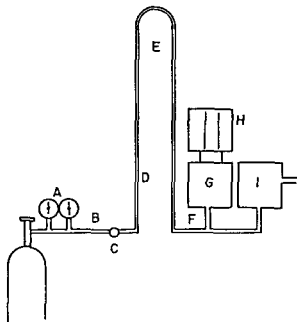
FIG. 15.7. Schematic representation of the gas chromatograph. The carrier gas is delivered from the flowmeter (A) into conduit (B) which carries sample introduced through plug (C) into adsorption column (D) and (E) from which it *passes through outlet tube* (F) *into detector* (G) which operates recorder (H). I is cell containing reference gas.

quantitation is made. The fastest moving gas reaches the detector first, then each of the others in succession according to their rate of movement. The apparatus is adaptable for microanalysis. With most devices the upper limit of sampling is 100 mgm. of liquid or ½ milliliter of gas. Liquid samples are usually introduced with a micropipette. The adsorbent is enclosed in a heated chamber in order to aid the vaporization of high boiling components (Fig. 15.7).

The concept by which the various components in a mixture of gases are separated by the adsorbent is sometimes referred to as the "plate" concept. The column may be likened to a fractional distillation still. The more volatile and less readily adsorbable substances are the first to issue from the column into the detector.
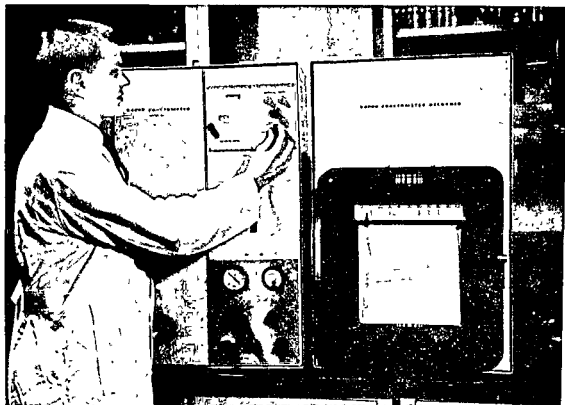
Fig. 16 7. Gas chromatograph in operation The recorder inscribes a peak for each gas present in the sample The height and base of each curve is proportional to the concentration of the gas present in the sample.

DETECTORS

Several types of detectors may be used. The katharometer (electrical conductivity) is used most frequently. The gases may also be carried into a hydrogen flame where they are burned under a sensitive thermocouple and the resulting difference in temperature is recorded. This technique is applicable to oxidizable gases. Temperature changes depend on the heat of combustion of the organic vapor. If the components are organic material they may be subjected to complete combustion and the resultant quantity of carbon dioxide is measured.

Chromatography is the method of choice for the separation of permanent gases related to anesthesia, such as nitrous oxide, carbon dioxide, oxygen and

cyclopropane. The adsorbents may be varied. Some are liquid. When a solid adsorbent is used the technique is referred to as *gas-solid* chromatography. The katharometer operates a direct writing recorder which inscribes a curve on a planograph. Quantitation is accomplished by determining the area beneath the curve and the base line. A mixture consisting of 3 parts of gas (A), two parts of gas (B) and one part of gas (C) in which (A) moves faster than (B) and (B) faster than (C) will produce the record shown in Figure 16.7. A is recorded first. The area beneath its curve is 3 times that of C and B is twice that of C.

LIMITATIONS AND USEFULNESS

The purity of a gas may be easily determined since only one peak or wave

will result on the tracing if the gas is pure and as many peaks as there are impurities if it is not. The disadvantages of the apparatus is that it is bulky and cumbersome and does not permit moment to moment sampling and cannot be used to quantitate gases in liquids.

Gas chromatography permits the analysis of inert gases for which agents to absorb them are unavailable and the analysis of those whose physical characteristics are too general to permit use of physical methods. Nitrogen, for example, is difficult to estimate in a mixture of nitrous oxide and oxygen. The chromatograph permits its analysis in the presence of any gas.

MASS SPECTROGRAPHIC METHODS

Gases may be analyzed by ionizing them and noting their behavior in a combination of an electric and magnetic field. The ionization is accomplished by using a beam of electrons. The ions of such an ionized gas are deflected by electrical and magnetic fields. The ionization takes place at low gas pressures. The ions are accelerated in such a way as to form a beam which passes through a slit into a chamber. In this chamber, they are first subjected to the influence of an electrical field, after which they pass into a magnetic field. The beam is deflected in one direction by the electric field as they pass through the slit into the analyzing chamber. They then pass through the magnetic field which causes them to be deflected in the opposite direction. By using this combination of a magnetic and an electrical field the ions constituting the beam are separated according to their specific charges. The magnitude of deflection depends upon the mass and the ratio of the charge on the ions. Ions of greater mass are deflected by the magnetic field to a less extent than the ions of lesser mass. The beam of ions is thus spread out into space forming the so-called *mass spectrum*. The mass spectrometer permits identification and quantitative determination of any gas irrespective of the number of other gases present. The method is specific, positive and extremely accurate. The apparatus, however, is complex and expensive. Skillful technicians are required for its successful operation.

MISCELLANEOUS METHODS

Numerous other methods for gas analysis are available which at some future date may be applicable to anesthesiology. The detection of isotopes of various gases used as tracer substances may become of practical importance. Condensation methods and distillation methods are among those which at the moment are of little importance but may later be of service.

Part II

ORGANIC CHEMISTRY RELATED
TO ANESTHESIA

Introduction

RELATIONSHIP OF ORGANIC CHEMISTRY TO ANESTHESIOLOGY

EVOLUTION OF DRUG CHEMISTRY

THE CHEMISTRY of anesthetic drugs is largely a study of organic chemistry. Few inorganic compounds are suitable for anesthesia. The evolution of drug chemistry has been gradual. Until recently most available therapeutic agents were galenicals or other biological substances whose active principles had not been isolated in pure form and whose mechanism of action was not understood. Many preparations could not be studied accurately and with precision because they were mixtures whose composition varied from specimen to specimen. As soon as the active principles were isolated from their sources and their chemical structures were determined, their synthesis became possible. The active principles, then, became available in pure form. Later, chemists, by modifying the side chains and groupings of these naturally occurring drugs, prepared a host of new compounds of varying degrees of potency and effectiveness. Encouraged by the results which ensued chemists ventured further and prepared compounds differing widely in structure from those found in nature. Thus, the galenicals and similar crude preparations have been pushed into the background and synthetic drugs now predominate in therapeutics.

CHEMICAL IMPLICATIONS OF DRUG-EFFECTOR RESPONSES

In the older therapeutics attention was focused primarily on the over-all effect and the end result produced by a substance. Little was known concerning its mode of action. As biochemistry developed and more became known about cellular structure and function, attention was directed towards the underlying mechanism of drug action. The earliest bits of evidence suggested that drugs act upon specific receptors on or in a cell. Thus, attention shifted from the gross response of the organism as a whole to the effect of drugs at the cellular level. As the response of the cell was studied, it became apparent that these receptors are probably endowed with specific, chemical groups and that certain drug actions are the results of interaction of specific side chains in the compound with reactive groups in the receptors. Thus, studies of drug action are now centered on interactions at the molecular level. This turn of events has brought biochemistry and organic chemistry together in the consideration of the chemistry and the action of drugs. No longer can one divorce one from the other in studying the pharmacological behavior.

BIOCHEMOMORPHOLOGY

Variations in some grouping or in a side chain of a particular drug may alter its effects profoundly. Such variations may enhance, attenuate, or nullify a particular response possessed by a drug. It was natural that this should all lead to the development of the branch of pharmacology known as biochemomorphology. This field is the study of the relationship of chemical structure of drugs to biological activity. When attention is directed primarily to drug action the study may be called pharmacochemomorphology. It has been possible, in some instances, to synthesize compounds with predicted biological activity. However, for every documented success there are scores of undocumented failures in this type of endeavor. Apparently, other factors besides structure are involved in drug behavior, which, at the present time, are not clearly understood.

RECEPTOR SITES AND DRUG ACTION

Early in the study of drug actions it became evident that molecules of drugs are attracted to and held at specific sites or receptors in a cell by forces of some sort. This focused attention upon the nature of these forces. It then became apparent that the manner in which *molecules are arranged in space plays an* important role in orienting these forces. The spatial arrangement of the reactive portions of the drug molecule together with the molecular configuration of the receptors in the cell have considerable bearing on physiological activity. Molecules of drugs appear to be accommodated into certain areas or slots in the receptors of the cell. The spatial arrangement of molecules may be three dimensional as well as planar. The distances between active atomic groups in

a molecule of a drug and groups on the cell site coincide. Activity is altered as these distances are altered. The distance between these active areas on a molecule is determined to a large extent by the number of intervening atoms and the forces holding the atom together. Discussion of spatial configuration and its influence on physiological activity will be deferred for the time being and will be presented in the following chapter. The manner in which union or bonding of atoms in molecules occurs will, however, be discussed.

BONDING

The union and holding together of atoms composing molecules and of molecules attached to each other is referred *to as bonding.* Four types of forces related to reactivity of molecules are involved in bonding. These are: (1) *Weak covalent bonding* (Chap. 1). This results in loose, reversible complexes. Strong covalent bonding usually results in stable, irreversible complexes. An example of this sort of bonding is found when sulphydryl (SH) groups of thiol compounds and arsenical drugs form thioarsenites. The reaction is reversible; therefore, the compound dissociates into the thiol compound and the arsenic derivative. (2) *Ionic bonding.* The molecule *dissociates into anions and cations,* each of which carries a charge in some portion of its structure. The active particle reacts with a grouping having a charge of opposite sign on the receptor in the cell. Tubocurarine, the active principle of curare, ionizes in solution into a basic quaternary ion with a positive charge which becomes attracted to a negatively charged grouping in the receptor. Besides purely ionic particles some molecules, though incapable of dissociation, are constituted so that they

behave like ions. They are polar molecules. In these electrostatic activity may be concentrated in one head of the molecule and thus have an electrical attraction for a grouping of opposite charge on another molecule or for an ion residing in a receptor. (3) *Van der Waals' forces* (Chap. 1). All molecules have some attraction for one another as a result of the mutual interactions of the electrons and nuclei. The nuclei (protons) of one molecule attract the electrons of another since they are oppositely charged. This is partly offset by repulsion of electrons of one molecule for electrons of another and nuclei of one for nuclei of another, since they are of the same charge and like charges repel. These forces are known as Van der Waals' forces. Van der Waals' forces increase as the molecular weight of a substance increases due to the increase in the number of electrons and nuclei in the structure. The bonding due to Van der Waals' forces is weak. Inert molecules, since they are not ionic, weakly covalent or polar, are believed to be bonded by Van der Waals' forces. (4) *Hydrogen bonding.* The hydrogen atom is composed of one proton and one electron. When it loses its electron to become a hydrogen ion it becomes a bare nucleus with a positive charge. The positive charge on a hydrogen ion is easily attracted towards molecules or atoms with a negative charge. A polar molecule having an unshared electron pair attracts the hydrogen ion and holds it closely forming a "loose" complex. The molecule of water, for example, has two hydrogen atoms which are attached closely to the oxygen atom. Two pairs of electrons are unshared and make water a polar substance. Therefore, water attracts hydrogen ions towards the unshared electrons which are located opposite the hydrogen atoms. Water, there-

fore, is capable of taking on four additional hydrogen atoms in this manner. The bonding holding this complex together is known as the *hydrogen bond.* The hydrogen atom, under appropriate conditions, may, therefore, be attracted simultaneously to two or more electronegative atoms instead of one and thereby acts as a bridge or bond between the two. Hydrogen bonding occurs with other elements. Most frequently it occurs with the most electronegative elements—fluorine, oxygen or nitrogen. This bonding is weaker than ordinary bonding but stronger than the Van der Waals' forces of intermolecular attraction. A substance like alcohol may react with the solvent water, and bond into a molecular particle of far greater size. This obviously would have some influence on physiological activity since it could change its effective size and reactivity in the cell.

RESONANCE

Another factor of possible importance in considering the influence of molecular structure on drug action concerns hybrid forms of a molecule. The chemical properties of some compounds indicate that their molecules have more than a single electronic structure of the valence-bond type. If a single electronic structure of the valence-bond type is assigned to a molecule it does not always represent its properties satisfactorily. At times two, three or even more valence-bond structures appear applicable. A concept called *resonance* has been introduced to explain how this comes about. In this concept a molecule of a substance may be a hybrid structure of two or more valence-bond structures. Various combinations of bonding and sharing of electrons are possible. A molecule having hybrid structures is indicated by writing

the various possible electronic structures together in brackets. In the case of carbon monoxide, for instance, three structures of valence-bond type appear possible. The resonating structures for carbon monoxide are, therefore, represented as follows:

$$\left[:C-\ddot{O}:\right] \quad \left[:C=\ddot{O}:\right] \quad [:C\equiv O:]$$
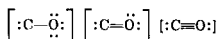
The energy level in each hybrid differs from the other and each resonates with the other. The transition from substances whose bonding is ionic to those whose bonding is covalent is not abrupt but instead occurs gradually. Some substances have covalent bonds but also have a certain amount of ionic character. These are referred to as *covalent bonds with partial ionic* character.

The replacement of an atom on a particular molecule by one which alters the intensity of the electrical field may attenuate or enhance a particular physiological attribute of a compound by modifying its bond strength and its reactivity to other substances. The activity of acetyl choline, for example, is dependent upon the ionic bonding between its cationic head and anionic grouping in the receptor. The conventional designation of the acetyl choline ion $(R_4N)^+$ represents only one state in a continued resonance between it and 15 other states of lesser charge density. Sixteen hybrid structures are possible. Substitution of the methyl groups of the cationic head of acetyl choline by hydrogen or other groups results in a progressive decrease in physiologic activity. This is due to a loss of charge density with progressive substitutions. The effective charge on the cationic head thereby is decreased. Substitution of ethyl groups reduces charge density and attenuates the cholinergic activity of the ion.

ISOTERES

Some molecules, even though they are dissimilar in structure, have similar electronic patterns. Because of this their chemical and physiological responses are the same. The concept indicating analogous physiological properties between a given molecule and others which have similar electronic patterns has been called *isoterism*. Such molecules are called *isoteres*. Isoterism may also be noted when dissimilar molecules have similar shapes or volumes. The central atom in the quaternary basic ion which reacts with the receptor in neuromuscular blocking agents, such as curare, is pentavalent nitrogen. Pentavalent arsenic, sulphur or other elements may replace nitrogen without loss of this pharmacological attribute. The isoterism may reside in certain specific links or groups of a molecule. Such dissimilar groups which manifest similarity of activity when interchanged or substituted one for another are called *isoteric groups*. In narcotics, for example, an isoteric group is present composed of a tertiary nitrogen atom, a dimethylene group, a quaternary carbon and a negative electrophilic carbon (Chap. 18). Additional factors which determine isoterism are the number and arrangement of electrons, the charge on the isoteric molecule, the type of bonding, dipole moments, resonance and tautomerism.

REACTIVITY AT RECEPTOR SITES

Anesthetics are usually referred to as volatile or non-volatile. The individual members of each of the two groups are similar but the two groups on the whole differ in pharmacological behavior. Vola-

tile drugs, in spite of widely differing chemical structures, appear to manifest a unitarian type of response in a given type of protoplasm. Volatile anesthetics are characterized by an inertness in the cell. No specific side chains are present on the molecule which react with cellular receptors. They act by some physicochemical mechanism in the cell. Nonvolatile drugs on the other hand respond differently. They are reactive with chemical groups in the receptors and become attached to structures in the cell. The ability to respond is nullified if the structure of the compound is altered, sometimes even in the slightest degree. They are believed to carry a particular grouping on a molecule which interacts with cellular receptors. This grouping has been referred to by some as the anesthesia-bearing or *anesthesiophore* or hypnophore group. This group becomes oriented to and forms a reversible union with the appropriate receptor in the cell by one of the bonding forces mentioned in the previous paragraph. Thus, it seems likely that chemically dissimilar substances which produce a uniform biological response in a given tissue do so by some physicochemical mechanism, and that compounds which possess a grouping or a linkage of similar structure or reactivity do so by interaction with other active groups in receptors on the cell. This is explained in more detail in subsequent chapters in the discussion of individual groups of drugs.

POTENCY OF DRUGS

The term potency is frequently used in discussions of chemical structure and physiological activity of drugs. Potency must be distinguished from effectiveness. Generally, potency refers to the number of molecules of a substance required to produce a given physiological change. Effectiveness is the completeness of response. Confusion frequently results because the term potency is erroneously used to indicate variations in effectiveness. Potency is also confused with duration of effectiveness. A few molecules may be completely effective over a short period of time. The compound is still considered potent. Many molecules may produce a partial effect over a long period of time. Relatively speaking the compound is impotent.

INTERDEPENDENCE OF BRANCHES OF CHEMISTRY

It is obvious from the foregoing discussion that it is not possible, when discussing drug action, to subdivide chemistry into categories such as inorganic, organic, physical, biological and so on. The anesthesia process and various phases of chemistry are all interwoven and cannot be divorced from each other. Nonetheless, the chapters in Part II which are concerned principally with the chemistry of drugs, are largely organic chemistry. However, the other aspects of chemistry and physics besides organic chemistry cannot be excluded. When indicated, the biochemical and physical influence of these compounds on cell receptors or their physicochemical behavior will also be considered along with their general chemical make-up.

The Chemical Nature of Anesthetic Drugs

ORGANIC VERSUS INORGANIC COMPOUNDS

MOST CENTRAL nervous system depressants are organic compounds. Notable exceptions are nitrous oxide, carbon dioxide, xenon, the salts of magnesium and the bromides. Practically all drugs used for, or as adjuncts to, anesthesia are synthetic. The narcotics, the belladonna alkaloids and certain other adjunctive drugs are active principles obtained from plants or glandular tissues. These, likewise, are organic substances. Organic chemistry, therefore, plays an important and significant role in anesthesia.

COVALENT BONDING

Organic compounds are chemical substances containing carbon. The element carbon has the valence of 4. It combines with 4 atoms of a univalent element 2 of a divalent element and in proportion with elements of higher valence. With hydrogen, such a combination results in methane, which has the following graphic formula:

$$
\begin{array}{c}
\text{H} \\
| \\
\text{H---C---H} \\
| \\
\text{H}
\end{array}
$$

One hydrogen atom shares its electron with one of the electrons of carbon. The two atoms, thus, share a pair of electrons. If the electrons are represented by dots methane would be represented as follows:

$$
\begin{array}{c}
\text{H} \\
\overset{..}{} \\
\text{H:C:H} \\
\overset{..}{} \\
\text{H}
\end{array}
$$

The bonding in organic compounds is *covalent* (non-polar). The field of force is concentrated between the atoms instead of being in space. The bonding force has a definite direction and specific bond angles exist between such carbons. The carbon atom possesses the unique property of being able to share its four electrons with other carbon atoms. This type of bonding permits the formation of chains containing fifty, sixty or more carbon atoms. These chains may be linear or *straight*, in a ring or *cyclic*, or they may be branched. As the number of carbon atoms increases in a compound the molecular weight, obviously, increases. In these molecules the electron systems of the atoms interpenetrate. The atomic nuclei are closer together than in those with ionic bonds. Absence of powerful fields of electrical forces externally accounts for many of the physical characteristics of organic compounds, such as low melting point, low boiling point, amorphous appearance, low solubility and so on.

240

ALIPHATIC HYDROCARBONS

Compounds containing carbon and hydrogen and no other element are called *hydrocarbons*. Straight-chained and branched-chained derivates in which all the valences are satisfied by hydrogen are called *alkanes*, or *paraffins*, or simply saturated hydrocarbons. Hydrocarbons of low molecular weight are volatile and depress the nervous system when inhaled and, therefore, are of interest in anesthesia. When two carbons join together and the rest of the valences are saturated with hydrogen,

ethane results—CH_3—CH_3

three, propane—CH_3—CH_2—CH_3

four, butane—CH_3—CH_2—CH_2—CH_3

five, pentane—CH_3—CH_2—CH_2—CH_2—CH_3

six, hexane—CH_3—CH_2—CH_2—CH_2—CH_2—CH_3

and so on. Such a series of compounds in which the increase in weight is one carbon atom plus two hydrogen atoms, and in which the same general configuration is maintained, is called a *homologous series*.

UNSATURATION

DOUBLE BONDED COMPOUNDS

It is possible for a pair of carbon atoms to share two electrons between them instead of one. Such bonding is referred to as a *double bond*. Electronically, a double bond is represented by two dots. The remaining electrons are shared with other elements. In the case of hydrocarbons the element is hydrogen. The compound is then *unsaturated*. In the usual graphic formula two lines are drawn between the carbons to indi-

cate such unsaturation and the linkage is called a double bond. Ethylene, representative of this group, is the simplest double bonded hydrocarbon, H_2—C= C—H_2. As in the case of the saturated hydrocarbons a homologous series forms with each successive addition of carbon atoms. Propylene, H_2—C=CH—CH_3, is the next higher homologue. Butylene H_2—C=CH—CH_2—CH_3, amylene, H_2—C=CH—CH_2—CH_2—CH_3 are higher straight-chained derivatives of a homologous series of unsaturated compounds known as the *alkenes*, or *olefins*. The ending "ene" on a compound indicates an unsaturated compound in contradistinction to the ending "ane" which indicates a saturated compound. More than one double bond may be present in an organic compound. The ending *"diene"* indicates the presence of two double bonds, *"triene"* three, and so on. Carbon atoms are numbered with Arabic numerals from the left end of a chain to the right or from the end nearest the most characteristic group in the structure of the molecule towards the right. These numerals are used to indicate where a double bond is placed or where an element or radical is located. In the following six carbon straight chain compounds there are two double bonds whose position would be designed as follows: 2,4,hexadiene CH_3—CH=CH=CH= CH—CH_3.

TRIPLE BONDED COMPOUNDS

Still greater unsaturation may be present in an organic compound so that two carbon atoms may be joined by a triple valence linkage. In such a case two carbon atoms share three electrons between them. Such a linkage is known as a *triple bond*. Electronically three dots represent the bond. Hydrocarbons with triple

bonds in their structure are known as *acetylenes* or *alkynes*. The simplest of a homologous series is acetylene, $H—C≡$ $C—H$, whose structure has two carbon atoms and one triple bond. This compound, like the double bonded compounds, is capable of further saturation with other elements. The addition of four more hydrogen atoms converts it to ethane. Different alkynes are formed by replacing the hydrogen atoms with various radicals. Their properties depend upon the number of carbon atoms and triple bonds composing their structure. Two triple bonds are indicated by the ending "diyne," three, "triyne" and so on. The location of triple bonds is designated by numbering in the same manner to that used for double bonds.

CYCLIC COMPOUNDS

Three or more carbon atoms may unite to form a ring-like structure or a *cyclic compound*. When the remaining valences of such a union are satisfied by hydrogen, a saturated cyclic hydrocarbon or *cycloalkane* results. The simplest member of such a homologous series is cyclopropane:

$$CH_2$$
$$CH_2—CH_2$$

The next higher member of this series is cyclobutane, then cyclopentane, cyclohexane, and so on. Cyclopropane and propylene have the same number of carbon and hydrogen atoms in their empirical formula, C_3H_6. Compounds which have the *same composition* but different structural arrangements and, therefore, different chemical properties are called *isomers*. Many of the cycloalkanes are isomeric with the alkenes or olefins.

Isomerism is also caused by the branching of the chains of carbon atoms.

Butane has, for example, two isomers, one called normal or n-butane and the other a branched chain or isobutane. The number of possible isomers increases as the carbon content of a compound increases. Isomerism is discussed in the latter part of this chapter.

ALKYL RADICALS

A group of atoms of one or several elements may be bonded in such a manner that the group acts as a single atom. Such a group acting as a unit has valence and, therefore, shares, donates or accepts electrons. Such atom groups are referred to as *radicals*.

If a hydrogen atom is removed from a straight chain saturated or unsaturated hydrocarbon, an *alkyl* radical results. Such a radical has a *valence of one*. It may, therefore, be attached in toto to another atom, as for example, oxygen, nitrogen or sulphur. Radicals cannot exist free but may be used to satisfy the valences of other carbon atoms or other elements. The radical derived from methane is called the *methyl radical* or group ($-CH_3$); that from ethane, the *ethyl* group ($-C_2H_5$); propane, *propyl* ($-C_3H_7$); butane, *butyl* ($-C_4H_9$), pentane, *pentyl* or *amyl* ($-C_5H_{11}$), and so on. If the radical is derived from a branched chain hydrocarbon, the prefix "iso" is placed before the name of the radical as happens, for example, in the case of the *isopropyl* group. Radicals may also be derived from unsaturated hydrocarbons. That derived from ethylene or ethene would be called *ethenyl*, $H_2C≡CH—$; that from propylene *propenyl*, $H_2C≡$ $C—CH_3—$, butylene, *butenyl*, $H_2—C≡$ $CH—CH_2CH_2—$ and so on up the series. The position of the double bond is indicated by placing the Arabic numeral of the carbon atom from which the bond originates before the name of the radical,

as for example, 2 butenyl, H_3—C—CH=CH—CH$_2$—. Radicals containing triple bonds are also known. The radical derived from ethyne or acetylene is designated as *ethynyl*, H—C≡C—; propyne or methyl acetylene, propynyl, HC≡C—CH$_2$— and so on.

CLASSIFYING ORGANIC COMPOUNDS

Organic compounds may be subdivided into four major classes—the *aliphatic, alicyclic, aromatic,* and *heterocyclic.*

Aliphatic compounds are saturated and unsaturated straight- and branched-chain compounds. *Alicyclic* compounds have one or more closed rings of carbon atoms. *Aromatic* compounds contain a special type of 6 membered ring known as the benzene ring. *Heterocyclic* compounds are closed cyclic structures containing other elements besides carbon in the ring.

AROMATIC COMPOUNDS

The six membered, fully saturated hydrocarbon is known as cyclohexane,
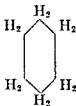
This is an alicyclic compound which has many properties of an aliphatic compound. Each carbon atom has two hydrogens. However, if each carbon were allocated one hydrogen apiece instead of two, the aromatic hydrocarbon benzene would result. Three double bonds would then be present in the molecule. The presence of three double bonds would suggest that the compound is highly unsaturated. However, many of the reactions of benzene are *not* those of an un-

saturated hydrocarbon. The carbons apparently are bonded together in an unusual manner. This bonding confers special properties to it and aromatic compounds which are derived from it. Its structure is designated by a hexagon with three double bonds at alternate carbons, . *Several benzene* rings may join together to give higher molecular weight aromatic hydrocarbons. *Two rings placed side by side form naphthalene,*

 ;

three *anthracene,*

 ;

or its isomer, *phenanthrene,*
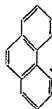
A hydrogen from one carbon of the benzene ring may be removed to form the *phenyl* radical

 , (C_6H_5).
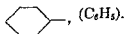
Radicals derived from benzene or its allies are termed *aryl* or aromatic radicals.

HETEROCYCLIC COMPOUNDS

Although any element may enter into the formation of heterocyclic compounds, the most common elements taking part in such formation are sulphur, nitrogen, and oxygen. Four carbons joined with oxygen, which is bivalent, sulphur, which is bivalent, or nitrogen,

which is tri- or pentavalent, yield the following five-membered rings
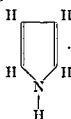
Furan   Thiophene   Pyrrole

If one carbon in the benzine ring is substituted by nitrogen, pyridine forms,

If the ring is completely hydrogenated, piperidine forms,
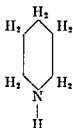
Piperidine

Both these structures are important in the makeup of compounds used in anesthesia. One carbon of one ring of naphthalene replaced by nitrogen results in quinoline

which is also important in anesthesia.

RADICALS AND SIDE CHAINS

Combinations of members of these four basic classes make possible hundreds of compounds. This comes about by the removal of a hydrogen atom from one of the carbon atoms to form a radical. This radical is placed in toto on some

position. Thus, an alicyclic, aromatic or heterocyclic radical may form a radical which is substituted on an aliphatic. Piperidine, for example, forms the *piperidyl radical;* naphthalene, the *naphthyl* radical. On the other hand an aliphatic radical may replace a hydrogen on an alicyclic, aromatic or heterocyclic compound. Examples would be ethyl cyclopropane, ethyl benzene and ethyl piperidine. Radicals placed upon the main or parent compound are referred to as side chains.

Certain radicals confer specificity to a structure in which they appear causing any compound having this particular grouping to react in a given manner when subjected to various tests. The carboxyl group, for example, confers acidic properties to an aliphatic, alicyclic, aromatic and heterocyclic structure. This group confers upon the compound the property of forming salts, and esters and water solubility. These radicals since they confer specific traits, serve to classify organic compounds. The *hydroxyl* (OH) group converts aliphatic, alicyclic, or heterocyclic compounds into *alcohols;* the aromatic hydrocarbons to *phenols.* The aldehyde group (CHO) converts all types into *aldehydes;* the *carboxyl* (COOH) into organic acids; the amino group (NH$_2$) into *amines;* the *carboxyl* (CO) into *ketones;* and so on. Several of these radicals may appear on a particular structure, each one conferring its own specific properties to the molecule independent of the other. Morphine, for example, has two hydroxyl groups, an oxy group and an amino group. The compound has the properties of an amine which makes it basic, a phenol, an alicyclic alcohol and an ether. Halogens, particularly chlorine and bromine, may replace hydrogens and convert aliphatic

hydrocarbons into *haloalkanes* which are important anesthetic drugs. Alkyl or aryl groups may satisfy the valences of oxygen, resulting in organic oxides or ethers, as exemplified by diethyl oxide, C_2H_5—O—C_2H_5. Thio ethers form when the valences of sulphur are so satisfied. These radicals and the compounds they form will be discussed in subsequent chapters.

ISOMERISM

TYPES OF ISOMERISM

Ordinarily the graphic formulas depict a molecule as being flat in one plane. Actually a molecule is arranged in space in three dimensions. The arrangement of the various side chains in space has considerable influence on pharmacological activity of a compound. This is particularly the case in certain isomers. There are two types of isomerism. In one type two or more compounds have the same empiric formulas but different structural formulas. This type is called *structural isomerism.* Isomers of this type are usually totally different from each other in physical, chemical and pharmacological properties. The other form of isomerism is known as *stereoisomerism.* In this form the structural formulas of the compounds are the same but the arrangements of the atoms in space are different. Two varieties of stereoisomerism are known, one known as *optical isomerism* and the other known as *geometric* or *spatial* isomerism.

OPTICAL ISOMERISM

Optical isomerism is caused by the presence of an asymmetric carbon atom on a molecule. An *asymmetric carbon atom* is one in which each of the four atoms or groups of atoms (radicals) satisfying the four valences of the carbon

atoms is different from the other. Such an atom causes plane polarized light passing through the substance to rotate from the vertical axis. This rotation may be to the right or to the left. Compounds which rotate plane polarized light to the right are called *dextro isomers;* those which rotate the plane of light towards the left are called *levo isomers.* An equimolar mixture of the two isomers causes each to neutralize the other and no rotation occurs. Such mixtures are called *racemic.* Optical isomerism is noted in many naturally occurring substances of plant and animal origin. The subject is dealt with in more detail in Chapter 20.

GEOMETRIC ISOMERISM

Geometric isomerism (also geoisomerism) is found when two carbon atoms are held together by a double bond. They, thus, cannot rotate freely about their mutual axis. The presence of two unlike substituents on each of the carbon atoms held together by the double bond gives rise to two different spatially arranged structures as the following structure illustrates:

$$
\begin{array}{cc}
R_1 \quad R_2 & R_1 \\
| \quad | & | \\
H-C=C-H & HC=C-H \\
& | \\
& R_2
\end{array}
$$
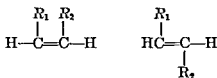
Geoisomerism is often referred to as *cis-trans isomerism.* It is neither associated with optical activity nor with the presence of an asymmetric carbon atom. When each of the dissimilar groups are both on one side of the double bond the compound is called the trans-form; when one is on one side and the other on the opposite side it is the cis-form. Usually, when such isomerism is demonstrated, the two resulting substances are referred to as the *alpha* or *beta* forms. Steroids

and certain alkaloids manifest this type of isomerism.

KETO-ENOL ISOMERISM

A certain form of isomerism which should correctly be classed under structural isomerism but is often treated as a separate entity is referred to as *keto-enol isomerism*. In certain molecules containing a carbonyl ($C=O$) group, hydrogen atoms manifest a certain ability to shift from adjacent atoms to the carbonyl group. The hydrogen becomes attached to the oxygen and the carbonyl group is converted to a hydroxyl. A double bond develops between the atom losing the hydrogen atom and the carbon atom recently possessed of the oxygen atom to which the hydrogen becomes attached. Thus, the compound exists either as a *saturated ketone* or an *unsaturated hydroxyl* isomer, each of which is relatively stable and readily interconvertible. This form of isomerism is encountered in the ureides, particularly the barbiturates. This form of isomerism is also referred to as *tautomerism*. The relationship may be depicted as follows:

$$-NH \qquad -N$$
$$\diagdown C=O \rightleftharpoons \diagdown C-OH.$$
$$-NH \qquad -NH$$
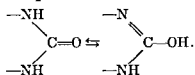
OTHER SPATIAL CONFIGURATION

The conventional manner of expressing the structure of organic compounds by graphic formulas depicts the arrangement of the atoms and radicals of a substance and their relationship to each other in one plane only. Such structural formulas do not indicate the absolute position of different groups and side chains. It is being recognized more and more that the spatial arrangement of the various groups of a molecule has considerable bearing on the physiological activity of a substance. Molecules may be arranged so that their atoms are in a single plane in a straight line. They may also be arranged in a single plane but the arrangement may not be linear. The molecule of water, for example, is bent at an angle. Cyclic structures likewise may be in a plane. However, there may be a strain at bond angles, so that the molecule is distorted and no longer planar but three dimensional. A six member ring, for example, could be bent so that its angles attempt to come together and the configuration would resemble a boat, or if the angles tend to spread apart they resemble a chair (Fig. 1.9). It may be possible that such configurations may influence drug action by modifying at-
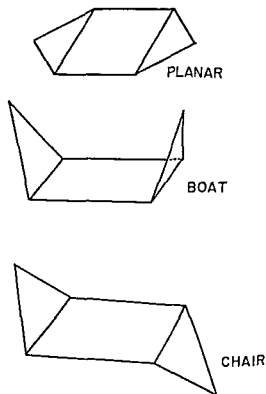
FIG. 1.9. Explanation in text.

tachment at receptors. More light is being shed on this aspect of chemistry by the precise methods of measuring atomic distances and determining spatial arrangement of atoms by newer methods which have been recently developed.

CLASSIFICATION OF ANESTHETIC DRUGS

Central nervous system depressants are classified in a number of ways. Clinicians classify them according to the route of administration, such as inhalational, intravenous, rectal and so on. Pharmacologists usually refer to them as being *volatile* and *non-volatile* depending upon whether or not they may be administered by inhalation or by routes other than inhalation. They also, at times, refer to the chemical grouping to which they belong, as for example, aliphatic alcohols, halogenated hydrocarbons, acids, ethers and so on. No classification embodies an all-inclusive description of a particular compound in a group. One must, therefore, select the term which best conveys the desired connotation. In this text compounds manifesting a central depressant action will be divided into aliphatic and non-aliphatic groups. The aliphatic compounds are subdivided into hydrocarbons, alcohols, aldehydes, ketones, ethers, acids and esters. Classification of non-aliphatic compounds is described in Chapter 16.

Hydrocarbons

TYPES OF HYDROCARBONS WITH ANESTHETIC ACTIVITY

THE ONLY organic gases possessing anesthetic properties which are used clinically are aliphatic or alicyclic hydrocarbons. Aromatic hydrocarbons are not anesthetic. Most volatile, aliphatic and alicyclic hydrocarbons are pharmacologically-active substances and, as a general rule, depress the central nervous system. The less volatile compounds which are sufficiently soluble to be absorbed also depress the nervous system. Hydrocarbons are inert in the body and undergo no chemical changes. Aliphatic hydrocarbons are either saturated or unsaturated. Saturated hydrocarbons do not interact with many reagents. Alkalies and acids exert no effect upon them. They, likewise, do not react with oxidizing agents, such as dichromate-sulphuric acid mixtures, permanganates, and chlorates. The lower molecular weight members of a homologous series are gases. Compounds composed of six or seven carbon atoms are low boiling point liquids, while higher molecular weight compounds tend to be semi-solid and solid substances (paraffins). One or more hydrogen atoms of a saturated hydrocarbon may be replaced by a halogen to yield an alkyl halide. Haloalkanes or halogenated hydrocarbons, as they are called, are important in anesthesia (Chap. 15). Unsaturated hydrocarbons

are more reactive chemically than saturated by virtue of the double or triple bonds. They are easily oxidized, add halogens, and enter into numerous chemical reactions not common to saturated substances. Triple-bonded hydrocarbons, as for example acetylene, tend to be more reactive than the saturated compounds. Hydrocarbons, in general, are poorly soluble in water (lipophobic) but highly soluble in lipoids (lipophilic) and miscible with many organic solvents (see narcotic potency, Chap. 27). As a general rule, water solubility of a hydrocarbon decreases as the molecular weight increases.

RELATIONSHIP OF STRUCTURE TO POTENCY

Many individual hydrocarbons in the aliphatic and aromatic series have been studied for narcotic potency. Methane, the simplest member of the saturated homologous series, was studied by Richardson (1867) who claimed it to be an effective anesthetic in animals. Subsequent investigators have been unable to obtain satisfactory anesthesia with concentrations as high as 87%. Richardson studied ethane also. This, too, is not a satisfactory anesthetic. Propane was studied by Brown and Henderson. They noted that concentrations of 93% or more were necessary for anesthesia. Butane, isobutane, and pentane were studied by

Stoughton and Lamson and found to be unsatisfactory. Saturated gaseous hydrocarbons may be disregarded since they are feeble anesthetics of no clinical value.

EFFECTS OF UNSATURATION

The introduction of double bonds into a hydrocarbon increases both potency and margin of safety. Unsaturation increases water solubility of a hydrocarbon while at the same time it maintains its lipophilic properties. This may have a bearing on increased potency. Thus, ethane is not satisfactory as an anesthetic but ethylene, its unsaturated counterpart, is quite satisfactory and is used clinically. The introduction of a double bond into propane forms propylene. This is more potent than ethylene as an anesthetic. Butylene is also more potent than butane. Triple bonds increase the potency still more. Acetylene is more potent than ethylene.

CYCLIC VERSUS STRAIGHT CHAIN COMPOUNDS

Cyclic compounds, excluding aromatic derivatives, are more potent than their straight chain counterparts. Cyclopropane is more potent than propane. It is also more potent and less toxic than its isomer, propylene. A comparison of the anesthetic potency of hydrocarbons, their relationships to their chemical structures is summarized in Table I.10.

GENERALIZATIONS CONCERNING STRUCTURE AND POTENCY

The following generalizations may be made regarding the relationship of structure, chemical properties and physiological activity of hydrocarbons. Volatility, water solubility, and flammability decrease as molecular weight increases. Volatility and solubility of branched-chain hydrocarbons are less than those of straight-chain isomers. Narcotic potency increases in each homologous series as the number of carbon atoms increases. The margin of safety is usually narrowed as molecular weight increases. Lipoid solubility increases with molecular weight. The oil/water partition coefficient becomes larger as molecular weight increases. Narcotic potency increases as the degree of unsaturation increases. Branching in an aliphatic chain causes a decrease in potency and an increase in toxicity. Increased nervous excitability, characterized by twitching of muscles, an increased irritability of cardiac automatic tissue, characterized by arrhythmias, and abnormal respiratory patterns, characterized by hyperpnea or gasping, are some of the manifestations of toxicity of higher molecular weight compounds. The range of flammability is greater with the lighter compounds. Hydrocarbons are inert in the body and are eliminated unchanged. Exceptions to the above generalizations do occur, of course.

Cyclopropane and ethylene are the only two hydrocarbons of the many which have been studied which are presently employed in clinical practice. Propylene, acetylene, and amylene have been tried in man but have been abandoned because of toxic effects, particularly on the cardiovascular system. A detailed discussion of individual hydrocarbons follows.

ETHYLENE

HISTORY

Although ethylene was discovered by Becher in 1669, its anesthetic properties were not adequately described until 1923 when Luckhardt and Carter, of Chicago, and Brown and Henderson of To-

TABLE I.10
THE GASEOUS AND VOLATILE LIQUID HYDROCARBONS WHICH HAVE BEEN
INVESTIGATED FOR ANESTHETIC PROPERTIES
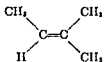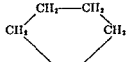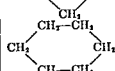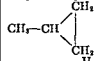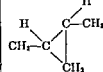
Name	Structure	M.W.	B.P. °C	Oil/H_2O Coeff.	Conc. for Anes. Vols. %	Effects and Remarks
Saturated						
Methane	CH_4	16	−160	19.3	97–300?	Not effective
Ethane	C_2H_6	30	−85		?	Not effective
Propane	C_3H_8	44	−37		?	Not effective
Butane	C_4H_{10}	58	−10		25	Not effective
Isobutane	$(CH_3)_3CH$	58	−1		45	55% lethal, circulatory depression
Neopentane	$(CH_3)_4C$	72	+9		50	Same as other alkanes
Unsaturated (Olefines)						
Ethylene	$H_2C=CH_2$	28	−103	13.2	85	*Effective clinically*
Propylene	$H_2C=CH—CH_3$	42	−17	52	40–50	Circulatory depression
Butylene α	$H_2C=CH—CH_2—CH_3$	56	−5		20–40	Circulatory depression
Butylene β	$CH_3—CH=CH—CH_3$	56	+1	173	30	Circulatory depression
Butylene γ	$H_2C=C=(CH_3)_2$	56	−6	144		Respiratory & circulatory depression
Amylene		70	35			Circulatory depression
Diolefines						
Allene	$CH_2=C=CH_2$	40	−22	27	20–36	Margin of safety narrow
Butadiene, 1:3	$CH_2=CHCH=CH_2$	54	−5	107	10–15	Respiratory and circulatory disturbances
Acetylenes						
Acetylene	$CH≡CH$	26	−88	2 2	50–85	*Useful on man*
Allylene	$HC≡C—CH_3$	40	−23		15	
Cyclic						
Cyclopropane		42	−34	34 3	20–35	*Effective clinically*
Cyclobutane	$CH_2—CH_2$ (ring)	56	−15		?	*Effective clinically*
Cyclopentane		70		49.3	8	Toxic
Cyclohexane		84		60.8	3–6	Toxic
Spiropentane		68		39.03	3–5	Toxic
Methyl cyclopropane		56	+5		15	Toxic
Dimethyl cyclopropane		70			10	Toxic

TABLE I.10—*Cont.*

Name	Structure	M.W.	B.P. °C	Oil/H₂O Coeff.	Conc. for Anes. Vols %	Effects and Remarks
Trimethyl cyclopropane		84			7	Toxic

ronto investigated its pharmacological activity in man and animals. *Ethylene is still used in many parts of the United States. Its use would be more widespread if clinicians did not fear the explosion hazard which attends its use.*

PREPARATION

Ethylene is one of the constituents of natural gas. It is the simplest member of the olefin series. Two carbon atoms are linked by a double bond. Ethylene adds two atoms of hydrogen to form ethane, its saturated homologue. This reaction is catalyzed by nickel or platinum.

$$H-\overset{H}{\underset{H}{C}}=\overset{H}{\underset{H}{C}}-H + H_2 \xrightarrow{Ni} H-\overset{H}{\underset{H}{C}}-\overset{H}{\underset{H}{C}}-H$$
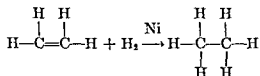
Ethylene may be prepared in one of several ways. In the laboratory it may be prepared by interacting ethyl bromide with alcoholic potassium hydroxide. Hydrogen bromide is removed and the unsaturated linkage results.
Ethylene to be used for anesthesia is

$$H-\overset{H}{\underset{H}{C}}-\overset{H}{\underset{H}{C}}-Br \xrightarrow[Alc.]{KOH} H-\overset{H}{C}=\overset{H}{C}-H + KBr + H_2O.$$

prepared by dehydrating ethyl alcohol with concentrated sulphuric or phos-

phoric acid at 150°C. or above. The reaction is expressed as follows:

$$H-\overset{H}{\underset{H}{C}}-\overset{H}{\underset{H}{C}}-OH \xrightarrow{H_2SO_4} H-\overset{H}{C}=\overset{H}{C}-H + H_2O.$$

Ethyl ether forms at lower temperatures if sulphuric acid is used. The alcohol may also be dehydrated by passing it with superheated steam at 360°C over aluminum oxide or other catalyst. The dehydration of ethyl ether by concentrated sulphuric acid also yields ethylene. The process of preparing the gas is known as the Cotton process.

Ethylene may also be prepared from natural gas by "cracking." *"Cracking" is the breaking of large hydrocarbon molecules into several molecules of lower molecular weight using heat and pressure.* Propane may be "cracked" to ethylene and methane. The reaction is as follows:

$$C_3H_8 \rightarrow CH_4 \uparrow + H_2C=CH_2 \uparrow$$

Other hydrocarbons may be used for "cracking" also.

PHYSICAL PROPERTIES

Ethylene is a colorless, flammable gas whose odor has been variously described as sweetish, musty, nauseating, ethereal, pungent and foul. The odor depends to some extent, upon the source of the gas and its accompanying impurities. Pure ethylene has a sweetish, ethereal odor. The gas prepared by "cracking" may have stronger and more disagreeable odors than that prepared from alcohol unless it is absolutely pure. The molecular weight of ethylene is 28.03. The gas is somewhat lighter than atmospheric air, having a specific gravity of 0.978 (air = 1). It diffuses quickly when it escapes into air and tends to float upward. Ethylene may be compressed to a liquid (B.P. 102–105°C.) and cooled to a solid (M.P. −181°C.). The pressure required for liquefaction is 42 atmospheres at 0°C. and 60 atmospheres at 10°C. The gas used for anesthesia is stored in the ordinary type of hollow steel cylinder. Since the critical temperature is 10°C. it is not liquid at room temperature. The viscosity is 100.8 micropoises at 25°C.

SOLUBILITY

Ethylene is sparingly soluble in water. As is the case with other gases, solubility decreases as temperature increases. At 0°C. one volume dissolves in 4 of water; at 25°C. one volume in 9 volumes; and at 37°C. 0 09 volumes in 1. The gas is highly soluble in the common organic solvents and in lipids. One volume dissolves in 0.05 volumes of ether at 15.5°C., one part in 0.5 volumes of alcohol at 25°C. The solubility in natural oils and fats is of interest as it may serve as an index of possible solubility in body lipids. Ethylene is a lipophilic anesthetic drug. The coefficient of distribution between olive oil and water is 14.4 at 37.5°C. The distribution coefficient for olive oil and blood is 9.3 at 37.5°C. The solubility in blood is greater than in water.

CHEMICAL BEHAVIOR

Ethylene, because of its double bond, is more reactive than its saturated homologue, ethane. Besides hydrogen, ethylene may also add halogens, various acids, and other substances. Such addition reactions remove the double bond and form a saturated compound. Hydrobromic acid adds directly to form ethyl bromide; sulphuric acid forms ethyl hydrogen sulphate. This latter reaction with sulphuric acid is important because it is employed to absorb the

$$H_2C{=}CH_2 + H_2SO_4 \rightarrow H-\overset{\displaystyle H}{\underset{\displaystyle H}{C}}-\overset{\displaystyle H}{\underset{\displaystyle HSO_4}{C}}-H$$
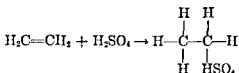
gas in volumetric analysis. This addition of the hydrogen sulphate group does not occur as readily with ethylene as it does with higher molecular weight olefins. One part of ethylene is required for each thirty parts of acid to carry the reaction *to completion so that it is quantitative.* The addition is facilitated by saturating *the acid with salts of metals, such as* those of nickel or silver.

Response to Permanganates

When ethylene is passed through a neutral potassium permanganate solution, it is converted into a water-soluble compound called ethylene glycol. Two hydroxyl (OH) groups add to each carbon atom. The double bond is lost:

$$H-\overset{\displaystyle OH}{\underset{\displaystyle H}{C}}-\overset{\displaystyle OH}{\underset{\displaystyle H}{C}}-H.$$
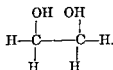
This reaction, characteristic of all light-weight olefins, does not occur with saturated and alicyclic hydrocarbons. The higher molecular weight olefins react with alkaline permanganate solutions to form higher molecular weight glycols. The glycols are ultimately oxidized to carbon dioxide and water, depending upon temperature and concentrations of the reacting agents. Ethylene is stable towards alkalies. It, therefore, undergoes no reaction when exposed to soda lime or barium-lime mixtures.

Uses

Ethylene is used for many purposes other than anesthesia. It is used for ripening fruits, as a fuel for torches for welding metals and as a starting material for many organic products. The purest grade is not necessarily used for industrial purposes. For anesthesia, however, the ethylene must be of the utmost purity. The favorite method of preparation is by the dehydration of alcohol. The acids and the alcohol must be of pure grade. The temperature and pressure must be rigidly controlled. As soon as the gas forms, it is cooled to remove alcohol, moisture, and any ether which may form. It is then passed through towers, washed with water, dried and cooled and compressed to a liquid at a pressure of approximately 2000 pounds per square inch. The liquid is allowed to boil and the vapor is packed in cylinders. The color adopted by the U. S. Bureau of Standards for ethylene cylinders is red.

Impurities

The impurities found in ethylene are either contaminants of manufacture or some accidental adulteration or decomposition subsequent to purchase. The impurities of manufacture are alcohol, aldehydes, ether, oxides of sulphur or phosphorous, nitrogen, oxygen, carbon dioxide, carbon monoxide, olefins, various paraffins, or acetylene. The type and amount depend upon the method of preparation. The United States Pharmacopeia recommends various tests for detection of impurities. A liter of the gas passed through 50 ml. of saturated barium hydroxide at the rate of two bubbles per second gives a white precipitate if carbon dioxide or sulphates are present. Bubbling a sample through an aqueous solution containing methyl red or other indicator of same pH range detects impurities of an acidic nature. Their color should not change. The oxides of sulphur, particularly the dioxide, are formed when sulphuric acid has been used as the dehydrating agent in manufacture. These react with water to form acids and cause the color of the indicator to change. The gas may be bubbled through ammoniacal silver nitrate to detect hydrogen sulphide. A black precipitate of silver sulphide forms. Hydrogen sulphide may form if sulphuric acid is used as the dehydrating agent. Aldehydes cause a black precipitate of metallic silver to form due to the reducing action of the aldehyde group. Phosphine, which may form when phosphoric acid is used as a dehydrating agent, likewise, gives a positive reaction with the silver reagent. The precipitate in this instance is white, however. Ethylene made by "cracking" may be contaminated by traces of acetylenes. These yield precipitates when passed into aqueous solutions of salts of heavy metals, such as mercury, copper and silver. The resulting compounds are known as acetylides. Acetylenes also form a white precipitate with the silver nitrate reagent.

Carbon Monoxide

One of the most dangerous contaminants of ethylene is *carbon monoxide*. Slight traces of carbon monoxide form as a by-product of manufacture, particularly when the "cracking" process is employed. Carbon monoxide has an affinity for hemoglobin three hundred times that of oxygen and forms a stable complex. The complex has a bright pink color. Once the carbon monoxide hemoglobin forms the complex is dissociated with difficulty. Therefore, the presence of even a minute trace, particularly if inhaled over a considerable length of time causes a high proportion of the available hemoglobin to be bound and unavailable for carrying oxygen. Consequently, an individual may become asphyxiated gradually without the appearance of cyanosis. Moreover, the presence of carbon monoxide hemoglobin in blood prevents the release of oxygen from whatever hemoglobin remains to carry oxygen. Carbon monoxide is removed from ethylene during purification by compression. The ethylene is compressed to a liquid at a pressure insufficient to liquefy carbon monoxide. The liquid is then drawn off and the gaseous carbon monoxide remains behind.

Carbon monoxide may be detected in ethylene qualitatively by exposing a quarter of a liter of the gas in a flask to a solution containing hemoglobin. The hemoglobin solution is prepared by adding 2.5 ml. of blood to 50 ml. of distilled water in which have been dissolved 50 mgm. of a mixture of equal portions of tannic and pyrogallic acids. Reduced hemoglobin and oxyhemoglobin are converted to various brown pigments when they react with the tannic and pyrogallic acids. The carbon monoxide hemoglobin complex is more stable than oxyhemo-

globin and does not react with the reagent and retains its pink color. This can be observed in the supernatant fluid after the mixture stands. A control test should be performed simultaneously with a carbon monoxide free sample of air for comparison. This reaction may also be used to determine the carbon monoxide quantitatively. The pink color of the supernatant fluid of the unknown is matched in a colorimeter with a standard prepared by exposing a known concentration of carbon monoxide to a given volume of reagent.

Carbon monoxide may be determined volumetrically using the Orsat or similar type of volumetric gas analyzer (Chap. 7). Oxygen must be absorbed first with a reagent, such as pyrogallic acid. Ethylene is then absorbed with concentrated (fuming) sulphuric acid. The carbon monoxide may be absorbed by an aqueous ammoniacal solution of cuprous chloride. Slight errors are introduced in this method because concentrated sulphuric acid may oxidize some ethylene to carbon monoxide or even to carbon dioxide. The quantities formed are insignificant. However, if precision is desired silver hydroxide may be used as the reagent instead. This converts carbon monoxide to carbon dioxide. Metallic silver forms which can be weighed

Nitrogen may also be a contaminant of ethylene. Nitrogen is such an inert gas that it is difficult to detect it in ethylene with simple apparatus. Its presence is objectionable because it dilutes the ethylene and decreases its effectiveness. If appreciable quantities are present nitrogen may be determined quantitatively as the residual gas using Orsat apparatus. The ethylene, oxygen, carbon dioxide and carbon monoxide must be absorbed with appropriate reagents. The

gas chromatograph, which has been employed successfully in the petroleum industry for *determining impurities* in hydrocarbon products, may be used for determining the purity of anesthetic hydrocarbon gases, such as ethylene, cyclopropane and *so on* (Chap. 7). The adsorption column separates all the components of a mixture and graphically portrays as peaks on the record for each component in a gas. Pure ethylene would give one peak. The presence of contaminants would give a peak for each contaminant.

BLOOD CONCENTRATIONS

The concentration of ethylene in blood may be *determined using the* manometric apparatus of Van Slyke and Neill or the iodine pentoxide train. If the Van Slyke is used determinations may be performed simultaneously with determinations for oxygen and carbon dioxide. However, no other volatile anesthetic *may be used along with ethylene;* otherwise errors are introduced. The ethylene is measured as the residual gas after the carbon dioxide and oxygen have been absorbed. Seevers and Waters have prepared a table of coefficients from experimental data which may be used for computation. *The pressures of the* residual gases are multiplied by these factors to obtain the concentration of ethylene in milligrams per 100 ml. of blood or other fluids.

The gas chromatograph which has been recently introduced into anesthesia research will probably replace all these methods since it can partition and quantitate each member of a mixture of gases (Chap. 7).

ABSORPTION AND ELIMINATION

Ethylene is not altered chemically in the body. It is, therefore, eliminated unchanged by exhalation from the lungs. *A slight amount (approximately 0.0019* mgm. per sq. cm. per hour) diffuses through the skin of man. Small amounts are lost through the kidney and gastrointestinal tract. Although practically all the ethylene in blood disappears within two minutes, traces are detectable in blood for several hours after recovery. This persistent trace is due to the slow elimination from the fatty tissues for which the gas has a great affinity.

Diffusion of ethylene from isolated lung lobules with occluded bronchi requires thirteen to twenty-three minutes. Air under similar circumstances requires *sixteen hours. Approximately two* and one-half times as much ethylene is carried by the red cells as is carried by the plasma during anesthesia. *The inhaled* concentration necessary for surgical anesthesia in man is approximately 80% to 85%. This mixture exerts a partial pressure in the alveoli of approximately 650 mm. Hg. The concentration in whole blood during surgical anesthesia in first plane of the third state averages between 120–180 mgm. per 100 ml. of blood.

DIFFUSION THROUGH RUBBER

Ethylene, like oxygen and carbon dioxide, diffuses through rubber. The rate of this diffusion is slightly faster than that of oxygen but only one-fourth that of carbon dioxide. Ethylene also dissolves in the rubber as do many other hydrocarbons.

FLAMMABILITY

Ethylene issuing from a gas jet burns with a slightly luminous flame. Mixtures of ethylene and oxygen and air are instantly combustible when ignited by

sparks and naked flames. Violent explosions result under such circumstances. A mixture whose composition ranges from 3.5% to 15% ethylene with air is explosive under ordinary conditions of temperature and pressure. The range is much wider if pure oxygen is used. Explosive concentrations range from 1.5% to 85% at ordinary room temperature and atmospheric pressure. The most violent and quickly induced explosions occur when mixtures are composed of 26% ethylene and 74% oxygen at room temperature (25°C.) and ordinary atmospheric pressure. Nitrous oxide does not reduce the range of flammability of mixtures of ethylene and oxygen. As low a concentration as 10% oxygen mixed with 47% ethylene explodes if the remaining 43% is nitrous oxide. The nitrous oxide supports combustion by releasing an atom of oxygen to carry on the oxidation. Nitrogen and helium used as diluents reduce the range of flammability of mixtures of ethylene and oxygen (Chap. 26). The reaction with ethylene is more violent than with other hydrocarbons. This in part may be due to the greater reactivity of the double bond. The products of combustion when ethylene is oxidized, as with other hydrocarbons, are carbon dioxide and water. These occupy approximately twice the volume of the original gases at room temperature and atmospheric pressure.

PROPYLENE

History

Propylene ($CH_2\!\!=\!\!CH\!\!-\!\!CH_3$) is not used clinically as an anesthetic. It is of interest because it is an isomer of cyclopropane and because, in a sense, it paved the way for the discovery of the anesthetic properties of cyclopropane.

Propylene is the next higher homologue to ethylene in the olefin series. Interest in the gas as an anesthetic was aroused following the experiments of Halsey, Reynolds, and Prout, Henderson and Brown. These workers investigated the effects of the gas on both man and animals. The drug is objectionable because it is toxic to the cardiovascular system. Serious arrhythmias appear as anesthesia progresses or is deepened both in man and animals. The gas is difficult to purify. Lack of uniformity of the experimental results reported was believed to be due, in part, to impurities in the specimens used. However, Summers and Adriani (1959) found that pure propylene produces serious arrhythmias and is not clinically suitable.

Preparation

Propylene may be prepared using a variety of methods. In the laboratory propyl alcohol may be dehydrated by a strong acid, such as sulphuric, in a manner similar to the preparation of ethylene. Another reaction utilizes propyl halides. These may be treated with alcoholic potassium hydroxide. The hydrogen and oxygen halide split off as in the method for making ethylene. Glycerol (1,2,3,trihydroxypropane) may be dehydrated with the aid of zinc dust to yield propylene. Commercially, propylene is obtained as a by-product when propane is "cracked." Propylene may form from its isomer, cyclopropane. In the presence of iron filings at 100°C., the ring is opened and 70% of the cyclopropane is converted to the open chain derivative.
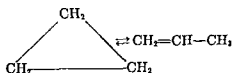
PROPERTIES

Propylene is a colorless gas possessing a somewhat sweet, ethereal odor which, in some respects, is similar to the odor of ethylene. The hydrocarbon is highly soluble in organic solvents and lipoids. The solubility in water is 0.136 volumes per unit volume at 20°C.; 7.217 volumes per volume of seasame oil at 20°C. The oil/water distribution coefficient at 20°C. is 52. Propylene is, therefore, lipophilic. Like ethylene, propylene possesses *greater solubility in blood than in water* (0.22 volumes in 1 volume of blood at 20°C.). The gas has the same specific gravity as cyclopropane (1.46, air = 1). The inhaled concentration required for anesthesia varies from 35% to 50% in animals and man. Induction of anesthesia with this concentration is rapid. Unconsciousness occurs within twenty seconds.

REACTIVITY

Propylene adds bromine to form propylene bromide, a saturated haloalkane. The reaction is 90% complete; the remaining 10% of the hydrocarbon is converted to a 1, 2, 3 tribromopropane.

Hydrobromic acid (HBr) forms an addition product. *The hydrogen adds to the end carbon and the bromine to the middle to form 2, monobromopropane.*

$$CH_2=CH—CH_3 + HBr \rightarrow CH_3—CHBr—CH_3$$

Propylene is more reactive chemically than ethylene. Concentrated sulphuric acid (not fortified with sulphur trioxide SO_3) absorbs 85% of a pure sample of hydrocarbon. Propylene is more readily oxidized than ethylene. High temperatures convert it to acetaldehyde, formaldehyde and acetylene. Acids polymerize propylene more readily than they do ethylene.

As a rule, iodine does not add readily

to the olefins. However, iodine does add to propylene. Hanus solution, a mixture of iodine in carbon tetrachloride, adds to the double bond and forms 1, 2 di-iodopropane.

FLAMMABILITY

The explosive range of propylene is 2% to 7% in air, and 3% to 45% in oxygen at room temperature (25°C.) and atmospheric pressure.

AMYLENE

STRUCTURE

Amylene is an unsaturated hydrocarbon. It was used for anesthesia (by inhalation) by John Snow in 1857. Waters and his associates studied the compound in man in 1937. They found that it caused serious arrhythmias and was not suitable as an anesthetic in man. Chemically, amylene is trimethylethylene—a five-carbon hydrocarbon with the following structure:

$$
\begin{array}{ccc}
CH_3 & & CH_3 \\
& \diagdown \quad \diagup & \\
& C=C & \\
& \diagup \quad \diagdown & \\
CH_3 & & H
\end{array}
$$
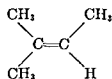
The hydrogen atoms on the ethylene molecule have been substituted by methyl groups.

PROPERTIES

Amylene is obtained by the dehydration of amyl alcohol in the presence of zinc chloride. It is a colorless, highly flammable liquid. It has a disagreeable odor. Its specific gravity is 0.66 at 15°C. It boils at 35–38°C. It is slightly soluble in water but highly soluble in organic solvents, such as alcohol and ether. It polymerizes to complex higher molecular weight hydrocarbons upon standing.

ACETYLENE

HISTORY

Acetylene is obsolete as an anesthetic. However, its comparative pharmacology is interesting. Attempts to popularize acetylene for anesthesia were not successful. Undesirable effects on the circulation discouraged its widespread use. It has been used extensively in Central Europe, particularly Germany, under the name Narcylene.

STRUCTURE

Acetylene is a triple bonded hydrocarbon. Structurally it is ethane minus four hydrogen atoms or ethylene minus two hydrogen atoms. It was first described by Davy in 1836 and later by Berthelot who prepared it by sparking carbon electrodes in an atmosphere of hydrogen.

$$2C + H_2 \rightarrow HC\equiv CH$$
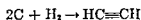
PREPARATION

The gas may be prepared in the laboratory by reacting ethylene dibromide with potassium hydroxide in alcohol. Two molecules of hydrogen bromide are removed from the molecules in the reaction:

$$\underset{\substack{| \\ H}}{\overset{\substack{Br \\ |}}{H-C}} \underset{\substack{| \\ H}}{\overset{\substack{Br \\ |}}{-C-H}} \quad \xrightarrow[2KOH]{HCl} \quad HC\equiv CH \uparrow + 2KBr + 2H_2O.$$
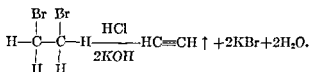
Commercially acetylene is prepared by reacting calcium carbide with water.

$$CaC_2 + 2H_2O \rightarrow Ca(OH)_2 + HC\equiv CH.$$
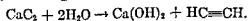
Calcium carbide is prepared by fusing coke with lime.

Commercial acetylene contains many impurities which cause it to be unfit for anesthesia in man.

PROPERTIES

Pure acetylene is a colorless gas which possesses a garlic-like, pungent odor. Impurities impart an additional unpleasant strong odor. Acetylene dissolves in approximately its own volume of water at 20°C. (1.042 cc. per ml.). Acetylene is highly soluble in acetone—31 volumes dissolve in 1 volume at 760 mm. Hg pressure and 20°C. At 12 atmospheres 12 volumes dissolve in 1 of acetone at 20°C. The gas explodes spontaneously when compressed. As little as 2 atmospheres pressure may cause the reaction; therefore, it cannot be stored in cylinders as a compressed gas or liquid. The high solubility in acetone is utilized in storage and dispensing the gas. The gas compressed under 26 atmospheres at 20°C. yields a liquid having a specific gravity of 0.45. Acetylene is unique in that its solubility in human blood is less than in water —0.965 volumes per unit volume of blood. The oil/water distribution coefficient is 2.2.

FLAMMABILITY

The formation of acetylene is an endothermic reaction. Therefore, considerable heat is liberated when it is oxidized. For this reason, it is employed as a fuel when high temperatures are desired. When the oxygen supply is limited acetylene burns with a smoky yellow flame. Mixtures of acetylene and air explode with violence. The flammable range is 2.8% to 40% in air; 2.8% to 85% in oxygen.

REACTIVITY

Three molecules of acetylene heated above 150°C. with a catalyst (quartz) polymerize to benzene.

$$3C_2H_2 \rightarrow \bigcirc$$
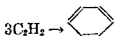
As is the case with other unsaturated hydrocarbons hydrogen, halogens and other substances add to acetylenes to form saturated compounds. In aqueous solutions acetylene has some of the properties of an acid and reacts with salts of heavy metals, such as copper and silver, to form acetylides. These are highly unstable compounds which explode spontaneously in the dry state. The reaction of formation of acetylides may be expressed as follows:

$$HC\equiv C-H + AgOH$$
$$\rightarrow HC\equiv C-Ag \downarrow + H_2O$$
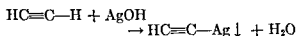
Acetylenes as a group are less stable than olefins and these in turn are less stable than paraffins.

IMPURITIES

The most probable and common impurities in anesthetic acetylene are phosphine (PH_3), hydrogen sulphide (H_2S), arsine (AsH_3), the inorganic gases, nitrogen, oxygen, and carbon dioxide and traces of various unsaturated hydrocarbons of higher molecular weight.

The gas used for anesthesia was dispensed in the same way as commercial acetylene—dissolved under pressure in acetone soaked asbestos sheets packed in cylinders. The acetone was removed at the time of use by passing the gas through water and over-activated charcoal. The process of removing acetone, which would be toxic if inhaled in large quantities, made the administration of acetylene cumbersome.

USES

The alveolar concentration necessary for unconsciousness in man averages 35%. Effective inhaled concentrations for surgical anesthesia average between 70% to 80%. The gas is eliminated rapidly, unchanged, from the body. The greater portion is exhaled within two minutes. However, traces may be detected in blood for as long as twenty minutes after discontinuing the inhalation. The gas diffuses rapidly from the peritoneal and pleural cavities. It also diffuses through the skin.

Acetylene has been employed to determine cardiac output by the indirect technique in man by Grollman.

QUANTITATIVE ANALYSIS

Acetylene is determined quantitatively by using the Haldane or other apparatus utilizing the absorptiometric technique if it is equipped with an additional absorption chamber for a reagent which absorbs the gas. Carbon dioxide is first removed by absorption with aqueous potassium hydroxide solution. The acetylene is next absorbed with mercuric cyanide solution ($Hg(CN)_2$) and oxygen is finally absorbed with alkaline pyrogallic acid solution. Mercuric acetylide,

$$Hg\begin{cases} C\equiv CH \\ \\ C\equiv CH \end{cases},$$

forms as a white precipitate during the absorption of the hydrocarbon.

OTHER ACETYLENES

The higher molecular weight acetylenes are too toxic for clinical use. Methyl acetylene, $CH_3-C\equiv CH$, which is found as a contaminant in commercial cyclopropane has been studied by Hender-

son. It possesses narcotic properties, but is toxic and, therefore, unsuitable for anesthesia.

CYCLOPROPANE

HISTORY

Cyclopropane was first prepared by the chemist Von Freund in Germany in 1882. Fifty years later its anesthetic properties were described by Henderson and Lucas, of Toronto. They noted that cyclopropane was one of the impurities in propylene in which they were primarily interested. They found the "impurity" to be more effective and less toxic than propylene and, therefore, continued to investigate its properties experimentally in animals. The drug was introduced into clinical anesthesia by Ralph M. Waters and his coworkers in 1933 at the University of Wisconsin. Cyclopropane, also known as trimethylene, is the simplest member of the alicyclic hydrocarbon series. The cyclopropane molecule is a saturated ring structure containing three carbon atoms. It is isomeric with propylene, into which it may be converted by heat in the presence of a catalyst.

PREPARATION

Ordinarily cyclopropane may be prepared by treating 1,3,dibromo- or dichloropropane with sodium or zinc which removes the bromide and causes the closure of the ring. This is the reaction used by Freund. It may be written as follows:

$$H-\overset{\overset{\displaystyle H}{|}}{\underset{\underset{\displaystyle Br}{|}}{C}}-\overset{\overset{\displaystyle H}{|}}{\underset{\underset{\displaystyle H}{|}}{C}}-\overset{\overset{\displaystyle H}{|}}{\underset{\underset{\displaystyle Br}{|}}{C}}-H \rightarrow \quad \underset{H_2C\underline{\quad\quad}CH_2}{\overset{CH_2}{\diagup\diagdown}} + ZnBr_2$$
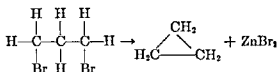
If 1,2,dibromopropane is used, propylene forms. In the commercial preparation of

the gas, 1,3,dibromopropane is treated with zinc and alcohol at carefully controlled temperatures and pressures. The gas is more expensive to prepare than ethylene or nitrous oxide. It would be impractical from an economic standpoint if it were used by other than the rebreathing technique. Haas and his coworkers found a simple method of preparing 1,3,dichloropropane (having the chlorine atoms on the terminal carbon atoms) without contamination with 1,2,-dichloropropane (having chlorine upon the middle atoms).

$$H-\overset{\overset{\displaystyle H}{|}}{\underset{\underset{\displaystyle Cl}{|}}{C}}-\overset{\overset{\displaystyle H}{|}}{\underset{\underset{\displaystyle Cl}{|}}{C}}-\overset{\overset{\displaystyle H}{|}}{\underset{\underset{\displaystyle H}{|}}{C}}-H$$
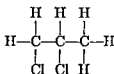
This had been difficult to accomplish previously. The closure of the ring is then carried out in the same way as it is with dibromopropane. Sodium, zinc, or magnesium may be used. With this process commercial propane may serve as the starting point thereby reducing the cost.

PROPERTIES

Cyclopropane is a pleasant, sweet-smelling gas, which is slightly irritating when inhaled in concentrations greater *than 50%. It has a molecular weight of* 42.078 and a density of 1.42 (air = 1). The gas is heavier than air and tends to fall downward before diffusing into the room atmosphere. Its critical temperature is 124.6°C. and critical pressure is 54.2 atmospheres. Cyclopropane liquefies at a pressure of 75 lbs. per sq. in. at 20°C. It boils at —32.89°C. and freezes at —127°C. The density of the liquid is 0.6807 gm./ml. at its boiling point. The latent heat of vaporization at its boiling point is 113.9 calories. Van der Waals constants are a = 8.280, b = 0.752. The viscosity at 0°C. is 80.7 micropoises. At

40°C. it is 92.3 micropoises. Cyclopropane is soluble in alcohol, benzene and other organic solvents. It is lipophilic and highly soluble in oils and fats. At 37.5°C. it has an oil/water partition coefficient of 34.43. At 37.5°C. 6.140 volumes are soluble in 1 of olive oil, while 0.179 are soluble in 1 of water. At 25°C. 0.255 parts are soluble in 1 of water. The solubility in human oxalated blood at 37.5°C. is 0.402 volumes of gas in 1 of blood—almost twice the solubility in water at the same temperature. In view of this greater solubility in blood, the oil/blood coefficient is less than the oil/water coefficient (15.3). During clinical anesthesia, the erythrocytes contain two and one-half times more cyclopropane than plasma. Cyclopropane is soluble in and diffuses very readily through rubber. The air/blood ratio at 34°C. is 0.4 in blood to 1.0 in air. This varies with the percent cell volume (hematocrit).

CHEMICAL REACTIVITY

Chemically, cyclopropane has some of the properties of a saturated hydrocarbon and also some of an unsaturated hydrocarbon. It is relatively resistant to oxidation by potassium permanganate or potassium dichromate-sulphuric acid mixtures. It is not affected by alkalis. It is stable in the presence of soda or barium-lime mixtures. Cyclopropane readily isomerizes to propylene in the presence of catalysts. If the gas is passed over iron filings at 100°C., 50% to 75% of the gas is converted to propylene. This could be an important consideration if the gas, stored in iron cylinders, were exposed to high temperatures. It is doubtful that the environmental temperature in the storage room of hospitals would ever reach that of boiling water. However, cyclopropane does not isomerize under ordinary circumstances nor

does it polymerize under pressure when stored over long periods of time.

Cyclopropane is readily saturated and converted to the straight chain (normal) propane when mixed with hydrogen and passed over a heated nickel catalyst. Bromine adds to cyclopropane and reopens the ring to reform 1,3,dibromopropane. This is illustrated by the following reaction:

$$\underset{\substack{| \\ H_2C\text{------}CH_2}}{\overset{\substack{H_2 \\ | \\ C}}{\diagup\diagdown}} + Br_2 \rightarrow CH_2BrCH_2CH_2Br$$
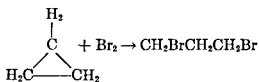
Hydrogen bromide also adds to cyclopropane and opens the ring to yield monobrompropane. Chlorine, on the *other hand, does not add to the ring.* Instead, it substitutes for one of the hydrogen atoms. The reaction yields cyclopropyl chloride and hydrogen chloride. Thus, the ring remains intact. The addition reaction with bromine is characteristic of unsaturated compounds; the substitution reaction with chlorine is characteristic of saturated compounds. Iodine neither adds nor substitutes to cyclopropane but does add to propylene. This dissimilarity between the two hydrocarbons is often used to differentiate propylene from cyclopropane. Cyclopropane does not decolorize iodine solutions; propylene does. As is the case with ethylene, fuming sulphuric acid (concentrated sulphuric acid with sulphur trioxide) absorbs cyclopropane in exactly the same manner as it does ethylene. The cyclic structure is disrupted and a hydrogen sulphate group adds to the hydrocarbon to form propyl acid sulphate.

$$\underset{\substack{| \\ H_2C\text{------}CH_2}}{\overset{\substack{CH_2 \\ | \\}}{\diagup\diagdown}} + H_2SO_4 \rightarrow CH_3\text{---}\underset{\substack{| \\ H}}{\overset{\substack{HSO_4 \\ | \\ C}}{}}\text{---}CH_3$$
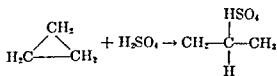
ANALYSIS

Cyclopropane may be analyzed quantitatively using the Orsat or other type of absorptiometric apparatus by absorption with sulphuric acid. Carbon dioxide and oxygen must be removed first by their respective absorbents (Chap. 7).

Cyclopropane may also be determined by combustion techniques. It may be oxidized to carbon dioxide and water with hot iodine pentoxide in the iodine pentoxide train (Chap. 7). This technique is employed for determinations in blood and other body fluids. The gas is usually distilled from blood or body fluid (as little as a 1 cc. sample) and conducted through a tube containing iodine pentoxide heated to 200–250°C. The carbon dioxide from the oxidized hydrocarbon passes off and is discarded. The iodine from the reduced iodine pentoxide is caught in a receiver containing potassium iodide solution and titrated with N/10 sodium thiosulphate solution and starch. The quantity of hydrocarbon present is calculated from the amount of iodine recovered, according to the following equation:

$$5C_3H_6 + 9I_2O_5 \xrightarrow[200°C.]{Heat} 15CO_2 + 15H_2O + 9I_2$$

$5C_3H_6 = 9I_2$, 1 mgm. $I_2 = .002$ mgm. C_3H_6
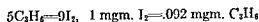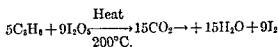
Cyclopropane in blood and other liquids may also be determined volumetrically by use of the manometric apparatus of Van Slyke and Neill and the modification described by Orcutt and Waters. The carbon dioxide and oxygen are first absorbed by their respective reagents and then the residual gas is measured (Chap. 7). No other anesthetic gas or volatile drug may be used for anesthesia with cyclopropane if results are to be valid because they interfere with analysis or add to the residual volume.

The gas chromatograph may also be used for analysis and determination of impurities (Chap. 7).

IMPURITIES

Impurities found in cyclopropane form during manufacture of the gas. Some may also be added by subsequent contamination. Propylene, allene, cyclohexane, nitrogen, carbon dioxide and certain halides, particularly brom or chlorpropanes, are possible contaminants. At the time of ring closure when the 1,3dibromopropane is used, an appreciable amount of propylene may form. Allene, which has two double bonds, may also form. Two molecules of dibromopropane may couple to form cyclohexane, as given at bottom of this page. The most prominent impurity appears to be propylene. Purification is accomplished by washing the crude gas with suitable reagents. It is then liquefied to further remove impurities.

The U. S. Pharmacopeia has outlined various tests for detection of impurities. Propylene, or any olefin, reacts with alkaline permanganate solutions to form gly-

cols. The double bond is removed. The resulting dihydric alcohol is oxidized further to various degradation products. Cyclopropane is inert and does not react with permanganates. This reaction may, therefore, be used to differentiate the isomers. The permanganate solution turns brown due to the formation of manganese dioxide (MnO_2) if propylene or other olefins are present.
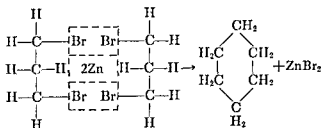
The reaction with potassium permanganate or iodine may be used for quantitative, as well as qualitative, determination of this contaminant. In performing the test a measured volume of gas is passed through a known quantity of N/10 potassium permanganate solution. The permanganate is converted to manganese dioxide in proportion to the propylene present. The unused permanganate is then determined by adding a measured quantity of sodium oxalate and performing a back titration with a standardized permanganate solution. The routine tests for carbon monoxide, carbon dioxide, and halogens may be carried out in the same manner as those described for ethylene. Up to 1% propylene is not considered objectionable.

ANESTHETIC CONCENTRATION

The inhaled concentration of cyclo-propane necessary for surgical anesthesia varies from individual to individual for a particular depth of narcosis. The average range is between 10–20%. The alveolar tension, therefore, ranges from 75–150 mm. Hg. The concentration in blood likewise varies from one individual to the next but ranges between 10–20 mgm. per 100 ml. of blood. Seevers found no evidence of polymerization or isomerization of cyclopropane by living tissues. Its elimination, like its absorption, is through the lungs. The major portion is eliminated within ten minutes although traces may be detected in the venous blood for several hours after anesthesia. Equilibrium between blood and non-lipoid tissues occurs quickly. The arterial and venous blood concentrations approximate each other within fifteen minutes after induction of anesthesia. The fat depots saturate slowly since, relatively speaking, they have a poor blood supply. They likewise desaturate slowly because, again, of the poor blood supply and also the lipophilic nature of the drug. This slow desaturation accounts for the traces which persist in blood for several hours after anesthesia has been discontinued. Cyclopropane diffuses through the skin as do ethylene and nitrous oxide.

Other Cylic Hydrocarbons

METHYL CYCLOPROPANE

The success of cyclopropane led to the study of other alicyclic hydrocarbons. monomethyl

$$H$$
$$|$$
$$C-CH_3,$$
$$H_2C----CH_2$$

dimethyl

$$H-C-CH_3$$
$$H_2C\quad\quad C-CH_3,$$
$$|$$
$$H$$

and trimethyl cyclopropane

H
|
C—CH₃
|
CH₃—C——C—CH₃
| |
H   H

CYCLOPENTANE

Cyclopentane (pentamethylene) is found in petroleum. It may be prepared by "cracking" cyclohexane. It may be prepared by the hydrogenation of benzene. It boils at 80.7°C. and melts at 6.4°C. The vapor is flammable. The flash point is —18°. The limits of flammability are 1.3–8.4% in air. The vapor has a pungent odor. The anesthetic properties of cyclopentane were described by Virtue and his associates in 1949. The anesthetic index is 1.97 (ether 2.07). The hydrocarbon, like cyclopropane and cyclobutane, causes sensitization of the heart to epinephrine. Neuromuscular phenomena were observed in animals. The concentration necessary for anesthesia is approximately 8%. It offers little promise of being clinically useful.

have been investigated by Henderson and found to possess anesthetic properties. The potency of these, like those of the straight chain compounds, increases as molecular weight increases. A concentration of 20% cyclopropane is required for anesthesia; 15% of the monomethyl, 10% of the dimethyl, and 7% of the trimethyl cyclopropane. These substances, however, cause cardiovascular disturbances which are more pronounced than those of cyclopropane. Mono- and dichlorcyclopropane are ineffective as anesthetics and cause pulmonary irritation.

CYCLOBUTANE

Cyclobutane (tetramethylene) was synthesized and studied pharmacologically by Krantz and his coworkers in 1948. It is prepared by the hydrogenation of cyclobutene in the presence of nickel at 100°C. The compound is a gas at room temperature and atmospheric pressure. It is not easily distinguished from cyclopropane by its odor. Its boiling point is 13.08°C.; its freezing point is —80°C. The Ostwald constant at 37° is 0.138. In olive oil it is 35.4 at 26°C. From a pharmacologic standpoint the hydrocarbon is similar in most respects to cyclopropane. It is a more potent anesthetic than cyclopropane but somewhat more toxic. The drug has been used clinically in man by Whitacre, Dripps and others but has nothing to offer over cyclopropane. For these reasons it has failed to gain popularity.

CYCLOHEXANE

Cyclohexane (hexamethylene) was also investigated by Virtue in 1949. It occurs in petroleum (0.5–1%). The hydrocarbon is a mobile, flammable liquid which boils at 49.3°C. and melts at —94°. It is more potent and toxic to animals than the cyclopentane. Less is necessary for anesthesia than when cyclopentane is used. It acts in accordance to the generalization that potency increases as molecular weight increases. The comparative quantities necessary for anesthesia in mice is 0.07 moles for cyclopropane, 0.003 for cyclopentane and 0.0013 for cyclohexane.

SPIROPENTANE

Spiropentane is a double cyclic structure consisting of two cyclopropane molecules with one carbon atom common to both rings.

$$\begin{array}{ccc} H_2C & & CH_2 \\ & \diagdown \; C \; \diagup & \\ & \diagup \; \diagdown & \\ H_2C & & CH_2 \end{array}$$
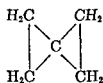
Actually it is an isomer of cyclopentane. The hydrocarbon is a liquid which boils at 30.03°C. and freezes at —107.5°C. Summers investigated its anesthetic properties in 1959 in mice and dogs. Three per cent produced anesthesia. The drug produced marked neuromuscular phenomena, respiratory and circulatory aberrations. It is noteworthy that pentane and all its isomers have little to offer as anesthetics.

HYDROCARBON MIXTURES (KEROSENE)

Mixtures of hydrocarbons are commercially available as gasoline, kerosene, mineral spirits and so on. These possess varying degrees of narcotic properties. The narcotic properties of aliphatic hydrocarbons increase from olefins to diolefins to naphthalenes. The toxicity varies with the composition of the mixture which in turn varies with the source of the petroleum from which the mixture is obtained. Inhalation of vapors of these mixtures produces acute intoxication characterized by narcosis, coma and convulsions. These hydrocarbons, like the others of purer form, are not metabolized in the body. They too are exhaled through the lungs. The rate of excretion varies with the volatility. Those of low volatility are also excreted into the urine or gastrointestinal tract.

Kerosene

Kerosene is of interest because it is an occasional cause of poisoning. Kerosene is a mixture of hydrocarbons obtained from crude petroleum. The true kerosene fraction distills at 175–275°C. All of the olefins and most of the aromatic hydrocarbons must be removed to enable the mixture to burn from a wick with a non-smoky flame. Since crude petroleum varies widely in composition depending upon the area from which it is obtained, the kerosenes likewise will vary widely in composition. The chief components are aliphatic, alicyclic, aromatic and aliphatic-aromatic hydrocarbons. In addition sulphur, nitrogen and oxygen containing compounds may be present.

Kerosene is frequently taken internally by children and causes poisoning. Kerosene poisoning is serious and often terminates fatally. The hydrocarbons are slowly absorbed from the intestines. Death is due to central depression from the blood borne kerosene or from injury to the pulmonary alveoli from the hydrocarbon present in vomitus which is aspirated when gastric lavage is attempted. Toxic effects on the heart, liver, and kidneys may also occur. The symptoms and intensity vary with the composition of the kerosene. Pneumonitis and pulmonary edema may follow the pulmonary damage. There is considerable evidence which indicates the pulmonary edema is due to minute traces of high boiling point compounds and to substances which are not hydrocarbon in nature. Data on blood levels and the nature of the toxic ingredient are meagre.

None of the hydrocarbon fractions in kerosene are metabolized. They are slowly eliminated via the lungs, kidney or gastrointestinal tract. Complete elimination may require days due to the low volatility of the hydrocarbons in the mixture.

Alcohols

DERIVATION

THE HYDROGEN ATOMS of an aliphatic hydrocarbon may be replaced by one or more hydroxyl (OH) groups to form *alcohols*. Marked changes in chemical, physical, and physiological properties result from this transformation. The hydrocarbon is altered so that the compound is chemically nearer to water. One may also look upon alcohols as compounds in which one hydrogen atom of water (H—OH) is replaced by an organic radical. The substitution of the hydroxyl group causes a decrease in the narcotic potency of hydrocarbons which possess narcotic activity. More than one hydroxyl group may be present on a multicarbon chain to form a *polyhydric alcohol*. This results in a still further decrease in pharmacological activity and, also as a rule, in a decrease in toxicity. If one hydrogen atom of methane is replaced by a hydroxyl group, methanol (carbinol), or if one wishes to use the common name, methyl alcohol (CH₃OH) results. Alcohols are often named after the radical they are capable of forming. The methyl radical results from methyl alcohol, ethyl from ethyl, butyl from butyl. The suffix "ol" indicates an alcohol also. Such a suffix is attached to the hydrocarbon from which the alcohol is derived. The prefix hydroxy also indicates the compound is an alcohol. Thus, methyl alcohol is also called methanol

and hydroxy methane. One hydroxyl group replacing a hydrogen atom of ethane gives ethanol or ethyl alcohol (C₂H₅OH); propane, under similar circumstances, forms propanol or propyl alcohol (C₃H₇OH); butane, butanol or butyl alcohol (C₄H₉OH); and pentane, pentanol or amyl alcohol (C₅H₁₁OH). Such a series of *monohydric alcohols* is known as a *homologous series*.

ISOMERS OF ALCOHOLS

In propane and higher carbon content homologues, the hydroxyl group may be on the terminal carbons. The compound formed with propane is termed normal propyl alcohol. The hydroxyl group may also be on the middle carbon atom, in which case the compound is called isopropyl alcohol. A chemical and pharmacologic difference exists between the two isomers. Those in which there is branching of the chain but in which the hydroxyl group is on a terminal carbon, are known as *iso alcohols*.

PRIMARY, SECONDARY AND TERTIARY ALCOHOLS

Alcohols are also classed as primary, secondary or tertiary, depending upon where the hydroxyl group is attached. Those which have the hydroxyl group attached to a carbon bearing two hydrogen atoms and a radical are *primary alcohols*

$$R-\overset{\displaystyle H}{\underset{\displaystyle H}{\overset{|}{\underset{|}{C}}}}-OH;$$

those in which the hydroxyl group is attached to a carbon atom bearing a hydrogen and two radicals are *secondary alcohols;*

$$R-\overset{\displaystyle H}{\underset{\displaystyle R}{\overset{|}{\underset{|}{C}}}}-OH$$

and those which have three radicals and no hydrogen atom on the hydroxyl bearing carbon are *tertiary alcohols.*

$$R-\overset{\displaystyle R}{\underset{\displaystyle R}{\overset{|}{\underset{|}{C}}}}-OH$$

Cyclic hydrocarbons may also have one or more hydrogen atoms replaced by hydroxyl groups to form *alicyclic* alcohols. In the aromatic series, such replacement results in compounds known as *phenols.* Heterocyclic alcohols form when a hydroxyl is placed on a heterocyclic nucleus.

Two hydroxyl groups are rarely ever attached to one carbon atom (see chloral, Chap. 15). Polyhydric alcohols are numerous, but the hydroxyl group in such compounds is attached to a separate carbon atom. Dihydric aliphatic alcohols are known as *glycols.* The simplest glycol is that formed from the two carbon molecule known as ethylene glycol

$$H-\overset{\displaystyle OH}{\underset{\displaystyle H}{\overset{|}{\underset{|}{C}}}}-\overset{\displaystyle OH}{\underset{\displaystyle H}{\overset{|}{\underset{|}{C}}}}-H,$$
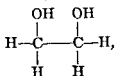
that from propane as propylene glycol and so on. The trihydric alcohol derived from propane is called glycerol. Hydroxyl groups may appear in compounds which have other radicals (carboxyl, aldehyde, amino), in which case the chemical and physiological properties are complicated still further. Carbohydrates, for example, are composed of polyhydric alcohols which have either ketone or aldehyde groups in the structure in addition to the hydroxyls.

STRUCTURE AND PHYSICAL PROPERTIES

Aliphatic hydroxy compounds are the only ones which possess narcotic potency. Aromatic alcohols or phenols do not and are distinctly caustic to cells. Phenol (hydroxy benzene) and a number of its allies produce a surface anesthesia on the skin (Chap. 21) but are otherwise highly toxic. Heterocyclic alcohols, likewise, are of no value. The introduction of the hydroxyl group into a hydrocarbon increases the water solubility and reactivity but decreases its volatility. Most alcohols are liquids; some are solids. Polyhydric alcohols have greater water solubility and lower volatility than monohydric. This increases with an increase in hydroxyl content of a given multicarbon structure. Refractive indices and boiling points increase as the molecular weights of the alcohols increase. Specific gravity increases as the carbon content increases. Branching the chain increases the water solubility and decreases the refractive indices and densities. The greater the degree of branching, the more pronounced are these effects. The seven carbon alcohol (n-heptyl alcohol) is less soluble and volatile than its isomer with one branch and this is less soluble and volatile than its isomer with several branches. Unsaturation in the molecule results in alcohols which are more volatile, less dense, but

more reactive than their saturated counterparts.

NARCOTIC POTENCY

The *narcotic potency of alcohols* is less than those of the hydrocarbons from which they are derived. This may be because they are less lipophilic and more hydrophilic than their related hydrocarbons (Chap. 27). The anesthetic potency of aliphatic alcohols increases as molecular weight increases until a maximum of eight carbons is reached. Higher molecular weight compounds show decreased activity. Water solubility likewise decreases with increase in molecular weight. If one designates the narcotic potency of ethyl alcohol in rats as 1; that of methyl alcohol is 0.59; of propyl alcohol, 2.33; of butyl alcohol, 3.56; and of amyl alcohol, 5.99. The toxicity likewise increases with the increase in molecular weight. Again assuming that of ethyl alcohol to be 1, methyl alcohol has a relative acute toxicity of 0.53; propyl alcohol, 3.27; butyl alcohol, 6.02; and amyl alcohol, 6.59. An increase in alkyl length of the chain is associated with increased lipophilic properties. Branching of the chain of an alcohol causes an increase in narcotic potency. Primary alcohols are less potent than secondary, and secondary alcohols less than tertiary. Increasing the number of hydroxyl groups in a compound decreases the narcotic potency. Unsaturation may increase both the toxicity and potency. Unsaturated tertiary alcohols are more potent than secondary. Triple bonded alcohols are more potent than double bonded. Unsaturated tertiary alcohols are more potent than primary. Halogenation of an alcohol markedly increases the narcotic potency (Chap. 15). Di- and tri-halogenated alcohols are less volatile than the nonhalogenated counterparts. They compose a group of useful hypnotics (see halogenated compounds). Richardson (1870) first observed the increase in potency of alcohols which follows the increase in carbon content of the molecule. His statement is often called *Richardson's Law*. Beecher, measuring cortical potentials in cats narcotized with various alcohols, has observed similar responses and confirmed this law. Unlike the hydrocarbons from which they are derived, alcohols are reactive in vivo as well as in vitro.

STABILITY

In vitro, primary alcohols subjected to oxidation by agents such as chromic acid or potassium permanganate are converted to aldehydes. Secondary alcohols yield ketones. Tertiary alcohols yield one or more miscellaneous compounds of smaller molecular weight because the molecule is disrupted into various degradation products. Alcohols may be attacked by various biochemical mechanisms in the body and completely altered. Ethyl alcohol, for example, is oxidized in the body to carbon dioxide and water. Alcohols possess high boiling points and low vapor pressures at room temperature. They cannot, therefore, be administered or excreted to any extent by inhalation. The higher molecular weight alcohols are either insoluble or toxic, or both, and are little used clinically. Of the alcohols, ethyl alcohol, amylene hydrate, pentynol (Dormison), a tertiary amyl alcohol and certain halogenated unsaturated alcohols (Chap. 15) are of clinical importance.

ETHYL ALCOHOL

Uses

Ethyl alcohol is a primary alcohol of low narcotic potency. Although not satis-

factory as a general anesthetic agent, it is of interest to the clinical anesthetist for a number of reasons: (1) ethyl alcohol is the basic raw material used to make many anesthetic drugs, such as ether, ethyl chloride, chloroform, vinyl ether, ethylene, tribromethanol, trichlorethanol, paraldehyde, chloral hydrate, and others; (2) the substance is present in small amounts in ether, vinyl ether, ethyl chloride, and is added as a stabilizer to chloroform; (3) some use exists for it as a premedicating agent by intravenous injection although it has never been successful enough to become popular; (4) alcohol is widely used in regional anesthesia and therapeutic nerve-blocking for injection and destruction of peripheral nerves and ganglia. Anhydrous or absolute alcohol is employed by most clinicians for this purpose.

Ethyl alcohol is ethane with a hydrogen atom replaced by a hydroxyl group, CH_3—CH_2—OH. Other names for it are methyl carbinol, ethanol, or hydroxy ethane.

SOURCES

The chief source of ethyl alcohol for human consumption is the fermentation of carbohydrates by yeast. Higher molecular weight carbohydrates are first hydrolyzed by enzymes to hexoses which in turn are fermented by the action of zymase to alcohol and carbon dioxide. Alcohol may also be synthesized by hydration of ethylene in the presence of a catalyst.

PROPERTIES

Ethyl alcohol is a clear, colorless, mobile and flammable liquid with a pleasant odor and somewhat pungent and burning taste. The molecular weight of ethyl alcohol is 46.05. Alcohol solidifies

at a very low temperature, —130°C. The refractive index is 1.361 at 20°C. The flash point is between 9° and 11°C. Anhydrous alcohol has a great affinity for water and rapidly abstracts moisture from the air. Ordinary alcohol (U.S.P.) contains approximately 95% alcohol by volume (92.3% by weight) at 15.5°C. It has a specific gravity of 0.816. The strength of alcohol is often expressed in "proof." Proof is usually double the per cent of alcohol by volume. One hundred proof indicates an alcoholic content of 50% by volume.

Affinity for Water

Most alcohol contains water. Absolute alcohol is necessary for regional block. The drug produces a long block by causing neurolysis. Absolute alcohol once prepared is difficult to maintain in its anhydrous state because of its affinity for water. Absolute alcohol corked in the usual manner absorbs water and can be preserved only in air-tight containers. The preparation of anhydrous alcohol is a tedious process entailing much labor. Alcohol as ordinarily distilled contains 50% or more water. Most of the water may be abstracted by refluxing and distillation with calcium oxide. The water combines with the oxide to form calcium hydroxide leaving the anhydrous substance as a residue. This process does not completely abstract all the water and slight traces always remain. Anhydrous calcium sulphate (Dririte) forms a hydrate and abstracts the water. As it is insoluble it does not contaminate the product. Commercially, dehydration of ethyl alcohol is accomplished by the fractional distillation of a mixture of alcohol and benzene. Three fractions are obtained. The first is a mixture of alcohol, benzene, and water, which boils at

64°C. The second is a mixture of benzene and alcohol which boils at 68°C. The third is pure alcohol which distills off at 78°C. The first two fractions are discarded.

A number of tests may be employed to distinguish the anhydrous alcohol from the hydrated product. If a pinch of anhydrous copper sulphate, which is a white powder, is added to a specimen it readily absorbs water to form the blue pentahydrate ($CuSO_4 \cdot 5H_2O$). The mixture should stand thirty minutes before it is concluded that the test is negative. Another test employs barium oxide which dissolves in anhydrous ethyl alcohol to form a clear colorless solution. The presence of the faintest trace of water produces a white cloud in the solution.

OXIDATION

Ethyl alcohol is readily oxidized in vitro to form acetaldehyde. Alcohol which has been standing in contact with air for any length of time oxidizes slowly and contains traces of acetaldehyde. Potassium permanganate and chromic acid solutions, ozone, peroxides, and other oxidizing agents convert it to acetaldehyde and small amounts of acetic acid. Chlorine, bromine, and iodine oxidize alcohol to aldehydes which are in turn halogenated and subsequently form chloral and bromal (see Chap. 15). These, in the presence of alkali, are converted to chloroform, bromoform, and iodoform. Alcohol may be esterified with mineral and organic acids. Dehydrating agents abstract a molecule of water from alcohol and convert it to ethylene. Metallic sodium reacts with alcohol to form sodium ethoxide and liberates hydrogen:

$$2C_2H_5OH + 2Na \rightarrow 2C_2H_5ONa + H_2 \uparrow .$$
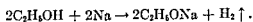
Sodium ethoxide is a valuable reagent used in organic synthesis to introduce the ethyl radical into various organic compounds. Sodium ethoxide reacts with water to form ethyl alcohol and sodium hydoxide:

$$C_2H_5ONa + H_2O \rightarrow C_2H_5OH + NaOH.$$
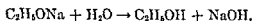
ABSORPTION AND ELIMINATION

Alcohol is rapidly absorbed from the gastrointestinal tract. Approximately 20% passes through the gastric mucosa, the remainder through the intestine, mainly the jejunum. Alcohol may be absorbed by the colon. The rate of absorption depends largely upon the concentration ingested and the dilution. Average amounts (50–60 cc.) are usually completely absorbed within two or three hours. Small amounts of the vapor may be absorbed by inhalation.

Alcohol is distributed uniformly to all tissues and body fluids. A longer time interval is required to attain the peak concentration in brain and spinal fluid. The disappearance is also slower than in other tissues. The concentration in brain tissues following death from acute intoxication varies from 0.27% to 0.50% by weight. Alcohol is oxidized in the *body presumably to carbon dioxide and* water. Oxidation proceeds at the rate of 8 grams per hour as judged by the disappearance from blood of an average-sized adult. One gram yields approximately 7 dietetic calories (7,000 ordinary) of heat. Large doses of alcohol may be incompletely oxidized to aldehydes, ketones, and acids which form as intermediate products and appear in the urine and exhaled air. Disulphuram (Antabuse) inhibits the oxidation of the acetaldehyde to carbon dioxide and water and thus causes it to accumulate

in the blood. The aldehyde causes symptoms of toxicity, such as vasodilatation, hypotension, etc. The aldehyde concentration may be ten times greater than ordinarily found after alcohol ingestion when this drug is used. Other anesthetics do not cause the formation of aldehydes and therefore may be used in the presence of disulphuram.

Oxidation of alcohol probably occurs in the liver. It is aided by enzymes. Insulin and glucose accelerate the oxidation of alcohol by tissues and its disappearance from blood. If small amounts of alcohol are taken, approximately 2% of the total is eliminated unchanged. If large doses are taken, the unchanged portion may amount to as much as 10% of the total. Most of the unchanged alcohol appears in the urine though some is eliminated through the lungs, in sweat, tears, and other secretions. The portion escaping by exhalation is usually one-half per cent of the total ingested amount. The concentration in the expired air bears a direct ratio to the blood concentration although it is considerably less. The numerical value for this ratio is believed to be constant and is used to calculate the blood concentration from the amount known to be present in exhaled air. The odor appearing on the breath is probably due to aldehydes and other products in the ingested beverage rather than to the alcohol itself. Alcohol appears in blood approximately five minutes after oral ingestion. Plasma contains twice as much by weight as the corpuscles. Since absorption proceeds at a more rapid rate than oxidation and elimination, alcohol tends to accumulate in blood and tissues. The blood level which indicates intoxication varies but usually lies somewhere between 200–300 mgm. per 100 ml. of blood. Ninety per cent of persons who have blood concentrations of 300 mgm. per 100 ml. are intoxicated according to clinical signs. Diuresis accompanies the ingestion of alcohol but only when the concentration in blood is rising. The diuresis may be the result of the depression of the pituitary with the subsequent decrease in circulating antidiuretic substance. Diuresis is not seen when the blood level is stationary or declining. The amount eliminated at a uniform rate of urinary secretion varies as the square of the amount ingested. The per cent of the total eliminated depends upon the quantity ingested.

ANALYSIS IN TISSUES

The quantitative determination of alcohol is important for medicolegal purposes. Numerous tests and devices have been devised for the purpose. Simple qualitative tests for alcohol are based upon the formation of iodoform, ethyl acetate, acetaldehyde, and other substances. Toxiological material, freshly obtained, is usually acidified with tartaric acid and steam distilled in the presence of mineral oil to recover the alcohol (Chap. 38). The distillate is then treated with sulphuric acid and potassium dichromate mixture and distilled once again to recover the acetic acid which forms. The distillate is titrated with standard sodium hydroxide solution and the amount of alcohol calculated is measured from the acid present. Haggard and Greenberg employed the iodine pentoxide train for determinations of alcohol on blood and other body fluids (Chap. 7). The alcohol is oxidized to carbon dioxide and water with the concurrent liberation of proportional amounts of free iodine and hydriodic acid. The latter are titrated with standard sodium thiosul-

phate and sodium bisulphite solutions, respectively, from which the amount of alcohol oxidized is calculated.

Sulphuric acid-dichromate mixtures may also be used to oxidize the alcohol. If a measured excess of the reagent is used, the reduced portion may be determined iodometrically or colorimetrically and the quantity of alcohol computed from the reduced portion.

CHEMICAL TESTS FOR INTOXICATION

An idea of the amount of alcohol in the brain may be obtained by examining blood, urine, saliva, spinal fluid, and expired air. The expired air is the easiest body material to obtain and is, therefore, used for measuring the alcoholic content in toximeter studies (Drunkometers). The test is based upon Henry's Law; namely, that the concentration of alcohol vapor in the alveolar air is proportional to the concentration dissolved in the blood, assuming that an equilibrium exists between blood and alveolar air. Exhaled air, obviously, is not pure alveolar air since it is mixed with air from the bronchi, trachea, etc. Therefore, it is also necessary to determine the partial pressure of carbon dioxide in the specimen. It is assumed that the alveolar air contains 5% by volume carbon dioxide and that this is a constant and normal in the adult. Thus, by measuring the carbon dioxide content of the sample it is possible, assuming that 5% carbon dioxide is in alveolar air, to compute the amount of alveolar air in the sample. It has been determined from data from a large series that the concentration of alcohol in grams bears a definite relationship to the carbon dioxide present in the alveolar air. Therefore, the percentage of alcohol in the blood may be obtained indirectly by determining the alcohol in

exhaled air simultaneously with the carbon dioxide content. The arithmetical expression used for computation is as follows: per cent of alcohol equals concentration of alcohol times 0.2 divided by grams of carbon dioxide times 100. The carbon dioxide is determined by absorption with an alkali, such as Ascarite (Chap. 5). The alcohol is determined by some technique utilizing the principle of oxidation.

A number of devices are available utilizing the above principle. One will be described here. The apparatus consists of a balloon into which the subject breathes a specimen of his exhaled gases of known volume. The air from the balloon is allowed to enter a branched tube which contains 6 grams of dehydrated magnesium perchlorate held in place by glass wool plugs. A second tube in series with this first one is filled with Ascarite which is also held in place by glass wool plugs. As the exhaled air passes through the train the perchlorate traps the alcohol vapors. The perchlorate also absorbs the moisture from the air. The Ascarite then absorbs the carbon dioxide. The alcohol absorbed by the perchlorate tube is then determined by oxidation by passing it into potassium permanganate solution. The degree of discoloration (reduction) of permanganate is an index of the alcohol present.

Unless this principle is properly applied this method of determination is subject to serious errors. The correct air-blood-alcohol distribution is 1/1300 at 37.5°C. and not at room temperature. One source of error is from the loss of alcohol in collecting the samples. This is usually combined with the condensed water vapor in the sampling bottles and lost. The concentration of carbon dioxide in alveolar air is difficult to deter-

mine, since air which is strictly alveolar air is difficult to obtain.

OFFICIAL PREPARATIONS

Alcohol is included in the U.S.P. Two forms are recognized: alcohol which contains 92–93% by weight and alcohol, diluted, which contains 41.5% by weight, or 48.9% by volume.

AMYLENE HYDRATE

CHEMICAL NATURE AND PROPERTIES

Amylene hydrate, also known as pentanol,

$$CH_3-\underset{\underset{C_2H_5}{|}}{\overset{\overset{CH_3}{|}}{C}}-OH,$$
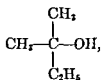
is a tertiary amyl alcohol. It was intro-

duced into therapeutics by Harnock and Meyer in 1894. The drug possesses mild hypnotic properties. Eight possible isomers of amyl alcohol are possible. Amylene hydrate is the most potent. The drug is largely employed as a solvent for tribromethanol. Its use as a hypnotic is obsolete.

Amylene hydrate is a clear, colorless liquid (M.W. 88.09) with an aromatic, camphor-like odor. The drug possesses a low vapor pressure at room temperature since it boils at 102° to 103°C. A white solid forms at −12°C. At 20°C. one part dissolves in eight parts of water. The substance is very soluble in benzene, alcohol, ether, chloroform and glycerine. Amylene hydrate may be ignited and burns but it does not explode since its flash point is high (20°C.).

PREPARATION

Amylene hydrate is prepared by chlorinating the hydrocarbon isopentane:

$$CH_3-\underset{\underset{H}{|}}{\overset{\overset{CH_3}{|}}{C}}-CH_2-CH_3 + Cl_2 \rightarrow CH_3-\underset{\underset{Cl}{|}}{\overset{\overset{CH_3}{|}}{C}}-CH_2-CH_3 + HCl$$
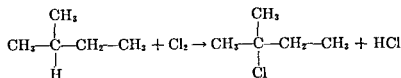
The chlorinated derivative is next hydrolyzed with acidulated water into trimethyl ethylene:

$$CH_3-\underset{\underset{Cl}{|}}{\overset{\overset{CH_3}{|}}{C}}-CH_2-CH_3 \rightarrow CH_3-\overset{\overset{CH_3}{|}}{C}=CH-CH_3$$
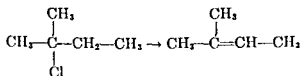
which is an unsaturated hydrocarbon. Hydration to amylene hydrate occurs readily by reacting the hydrocarbon with 50% ethyl alcohol and water:

$$CH_3-\overset{\overset{CH_3}{|}}{C}=CH-CH_3 + H_2O \rightarrow CH_3-\underset{\underset{OH}{|}}{\overset{\overset{CH_3}{|}}{C}}-CH_2-CH_3$$
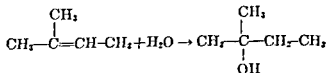
STABILITY

Amylene hydrate is easily oxidized by chromic acid and other oxidizing agents. Various degradation products form, depending upon the temperature, concentration, and other conditions. Ketones and aldehydes are the most common by-products, but acids may form also. The drug is stable if preserved in tightly-stoppered dark bottles which exclude light and air.

USES

The chief use of amylene hydrate is as a solvent for tribromethanol to form "avertin fluid." One gram of tribrometh-anol dissolves in ½ gm. of alcohol to form 1 cc. of fluid. This mixture is heavier than water and sinks to the bottom of the container. Amylene hydrate floats (S.G., 0.807). The hydrate is rarely employed as a hypnotic in clinical medicine inasmuch as more efficient drugs are available.

FATE

The metabolic fate of amylene hydrate differs from one species to the next. In man, the drug is eliminated unchanged by the kidneys. Some may be eliminated from the lung, but the vapor pressure of the alcohol at body temperature is too low to rely upon this channel for elimination. In animals the alcohol is conjugated with glucuronic acid and excreted into the urine.

METHYLPARAFYNOL

PROPERTIES

Pentynol (methylparafynol), a hypnotic without analgesic or anesthetic properties known under the proprietary name of Dormison (Schering), was introduced in 1951 by Margolin and his associates. This compound is a triple bonded six carbon alcohol. The bond is between the first and second carbon atom. The third carbon atom bears the hydroxyl group and also a methyl group. The full chemical name is 3, methyl pentynol 3. The compound is a tertiary alcohol. The substance is a liquid with a hydrocarbon-like odor which boils at 118-121°C.

FATE

The drug is readily absorbed from the gastro-intestinal tract. Ten minutes after an intravenous injection in an animal 20% of the dose may be recovered in the blood. None is present after two hours. The drug passes into muscle, fat and the brain. The drug is probably metabolized to carbon dioxide and water by the liver and kidney. None can be detected in the urine during the 24 hours after injection.

POLYHYDRIC ALCOHOLS

Polyhydric alcohols possess no hypnotic effects. The propandiols however are esterified with carbamic acid. These derivatives are used as ataractics (Chap. 20).

Aldehydes and Ketones

FORMATION OF ALDEHYDES AND KETONES

ALDEHYDES AND KETONES are compounds resulting from the oxidation of alcohols. The oxidation of a primary alcohol yields an *aldehyde;* oxidation of a secondary alcohol, a *ketone.*

$$2CH_3-\overset{H}{\underset{OH}{\underset{|}{\overset{|}{C}}}}-CH_3 + O_2 \rightarrow 2CH_3-\overset{}{\underset{O}{\overset{|}{C}}}-CH_3 + 2H_2O.$$
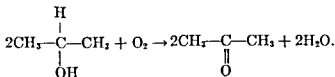
The oxidation of a tertiary alcohol results in various degradation products. The oxidation of an aldehyde may be looked upon as a dehydrogenation of the alcohol. The name "aldehyde" has been derived from this process (alcohol dehydrogenatus). Structurally, an aldehyde is a hydrocarbon in which one hydrogen atom is replaced by an aldehyde group,

$$R-\overset{}{\underset{O}{\overset{|}{C}}}-H.$$

The formation of an aldehyde group may be looked upon as the removal of two hydrogen atoms from the terminal carbon bearing the hydroxyl group of a primary alcohol. One hydrogen is derived from the hydroxyl group and one from the carbon atom. The *aldehyde group* is always written CHO, and not COH.

The hydroxyl group of a secondary alcohol is never on a terminal carbon. It is always located on a carbon which bears two radicals and one hydrogen atom. If a hydrogen atom is removed from both the carbon carrying the hydroxyl group and the hydroxyl group itself, the *ketonic* or *carbonyl* group results. This goes on during oxidation of a secondary alcohol.

Aldehydes and ketones, as such, play insignificant roles in anesthesia. Aliphatic aldehydes are mildly hypnotic. Potency and toxicity increase as molecular weight increases. The aldehyde group, as a rule, seems to confer irritating properties. Aliphatic aldehydes are neutral, colorless gases or liquids which are very soluble in water. Aldehydes are more volatile than the alcohols from which they are derived. Formaldehyde (HCHO) is the simplest member of the homologous series of aliphatic aldehydes. The substance is a gas which boils at —21°C. Methyl alcohol, from which it is prepared, boils at 68°C. *Acetaldehyde,* which is the next higher homologue of the straight chain series, is prepared from ethyl alcohol. This is a liquid which boils at 21°C. (alcohol B.P. 78°C.). Volatility and water solubility of aliphatic aldehydes decrease as their molecular weights increase. Oxidation

converts aldehydes to organic or carboxylic acids.

CHEMICAL BEHAVIOR OF ALDEHYDES AND KETONES

In addition to aliphatic aldehydes, one may also encounter alicyclic, aromatic, and heterocyclic aldehydes. An aldehyde group replaces a hydrogen atom from one of these. Benzaldehyde,

is the simplest member of the aromatic series of aldehydes. Certain narcotics are complex heterocyclic ketones (Chap. 18).

REDUCTION OF COPPER AND SILVER COMPOUNDS

The aldehyde group responds in a number of specific ways to certain chemical reagents. These reactions serve to differentiate it from other groups. These responses occur regardless of the type structure upon which the radical appears (i.e., aliphatic, alicyclic, aromatic or heterocyclic). Aldehydes are oxidized to acids by the oxides of heavy metals, particularly those of silver or copper. Tollen's reagent, which is prepared by dissolving silver hydroxide in ammonium hydroxide, provides the silver oxide. The latter compound, Ag_2O, is reduced to metallic silver which precipitates in a finely divided form. Cupric hydroxide, $Cu(OH)_2$, may be made water soluble by the addition of glycerine (Haine's solution). The formation of a complex tartrate ion (Fehling's solution), or complex citrate ions (Benedict's solution), occurs readily with cupric salts in the presence of alkalies. The copper in these cupric compounds is reduced to the cuprous state, aided by heat. Cuprous oxide,

which is red forms as a precipitate *bohydrates* are complex polyhydric hols which have, in addition to tl droxyl group, an aldehyde or a k group on one of the carbon atoms. respond to these tests, also.

FORMATION OF ADDITION PRODUCT

The aldehyde group adds or tal certain substances to form addition ucts. Sodium hydrogen sulphite, dium bisulphite ($NaHSO_3$) adds di and forms the addition product trated by the following reaction:

$$CH_3CHO + NaHSO_3 \rightarrow CH_3\overset{\displaystyle OSO_3}{\underset{\displaystyle H}{\overset{|}{\underset{|}{C}}}}-O$$
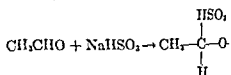
Bisulphite addition products are cr line precipitates, particularly formed from high molecular weig dehydes. This reaction frequent used to prepare aldehydes in pure since alkalies release the aldehyde the bisulphite. Ammonia may als to the aldehyde group to form an *hyde-ammonia* which is actuall amine. The formation of these a compounds is illustrated by the fo ing reaction:

$$R-\overset{\displaystyle H}{\underset{|}{\overset{|}{C}}}=O + NH_3 \rightarrow R-\overset{\displaystyle H}{\underset{\displaystyle NH_2}{\overset{|}{\underset{|}{C}}}}-OH.$$
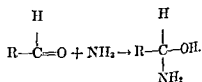
Chloral (Chapter 15) forms an ¿ tion product of this type which has notic properties. Hydrogen cy² (HCN) also may add to form *cyⁿ drins*:

$$RCHO + HCN \rightarrow R-\overset{\displaystyle H}{\underset{\displaystyle CN}{\overset{|}{\underset{|}{C}}}}-OH.$$
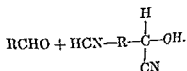
Aldehydes may be transformed into alcohols by the addition of two hydrogen atoms to the hydroxyl group. This may be accomplished by the aid of metallic catalysts, such as copper, nickel, or zinc. The alcohol from which the aldehyde was originally derived is formed:

$$RCHO + 2H \rightarrow RCH_2OH$$
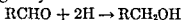
Substitution reactions occur between aldehydes and certain compounds containing the NH_2 group, chiefly the hydrazines and hydroxylamines and semicarbazides to form hydrozones, osazones, oximes and semicarbazones respectively. Two hydrogen atoms of the amino group combine with the oxygen in the carbonyl group of the aldehyde radical to form a molecule of water.

$$R-\overset{\overset{\displaystyle H}{|}}{C}=\!\!O + H_2N-OH$$
$$\rightarrow R-\overset{\overset{\displaystyle H}{|}}{C}=N-OH + H_2O$$
(Oxime)

$$R-\overset{\overset{\displaystyle H}{|}}{C}=\!\!O + H_2N-NH_2$$
$$\rightarrow R-\overset{\overset{\displaystyle H}{|}}{C}=N-NH_2$$
(Hydrazone)

$$R-\overset{\overset{\displaystyle H}{|}}{C}=\!\!O + H_2N-\overset{\overset{\displaystyle H}{|}}{\underset{\underset{\displaystyle O}{\|}}{C}}-NH_2$$
$$\rightarrow R-\overset{\overset{\displaystyle H}{|}}{C}=N-N-\overset{\|}{C}-NH_2$$
$$\qquad\qquad\;\; \overset{|}{H}\;\; \overset{|}{H}\;\overset{\|}{O}$$
(Semi-carbazone)
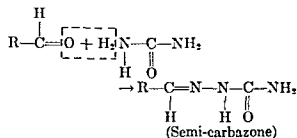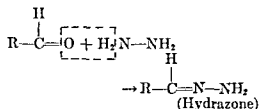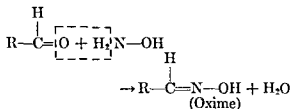
These derivatives are high-boiling-point liquids or solids, depending upon the molecular weight of the aldehyde from which they are formed. They are of interest because they possess *individual* boiling or melting points and may be used for the identification of aldehydes.

POLYMERIZATION OF ALDEHYDES

One characteristic of aldehydes is their tendency for a number of molecules to combine with one another to form new compounds. Such a reaction in which several molecules of a particular compound unite to form a heavier molecule is known as *polymerization*. If formaldehyde in aqueous solution is evaporated to dryness it yields *paraformaldehyde* $(HCHO)_n$. The exact number of aldehyde molecules in this compound is not known. *Acetaldehyde is the* aldehyde of most interest to the anesthetist because it forms the basis of several hypnotic drugs. It readily polymerizes in the presence of traces of sulphuric acid at room temperature to a liquid known as *paracetaldehyde*, or paraldehyde $(CH_3CHO)_3$. Three molecules of acetaldehyde interact to form this polymer. If the reaction is carried out at $0°C.$, a solid substance metaldehyde $(CH_3CHO)_4$ forms. The exact number of acetaldehyde molecules required to form metaldehyde is not known.

PARALDEHYDES

Other aliphatic aldehydes may be converted to *paraldehydes*. Paraldehydes possess a cyclic structure composed of three carbon atoms alternating with three oxygen atoms. Their formation is illustrated by the following general reaction:

$$3CH_3-CHO \rightarrow$$

$$\begin{array}{c} \overset{\displaystyle H}{\underset{\displaystyle |}{}} \\ C-CH_3 \\ \diagup \quad \diagdown \\ O \qquad O \\ | \qquad\qquad | \\ H-C \quad\;\; O \;\;\quad C-H \\ | \qquad\qquad | \\ CH_3 \qquad\quad CH_3 \end{array}$$
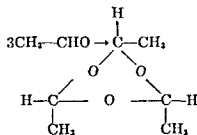
No free aldehyde group is present anywhere on the ring. Therefore, paralde-

hydes do not respond to the tests for the aldehyde group. Paraldehydes are in reality *polyethers* (see ethers).

Paraldehydes possess hypnotic properties. They are less volatile and irritating than aldehydes. Knoefel examined the series of aliphatic paraldehydes through parabutyraldehyde. He found that paracetaldehyde was the least toxic and most effective. Metaldehyde possesses hypnotic properties. However, it is more toxic than paraldehyde and not used clinically. Boiling polymers of aldehydes with dilute mineral acids regenerates the respective aldehydes which originally entered in the polymerization reaction.

ALDOLS

In the presence of dilute aqueous alkalies, aldehydes undergo a reaction known as the *aldol condensation*. Two molecules of the aldehyde interact in such a manner that the hydrogen atom from the alpha carbon on one molecule (the carbon bearing the CHO) "migrates" to the oxygen of the aldehyde group on the other molecule converting it to a hydroxyl group. The reaction between two molecules of acetaldehyde is illustrated as follows:

$$CH_3CHO + CH_3CHO \rightarrow CH_3-\overset{\overset{\displaystyle H}{|}}{\underset{\underset{\displaystyle OH}{|}}{C}}-\overset{\overset{\displaystyle H}{|}}{\underset{\underset{\displaystyle H}{|}}{C}}-CHO$$
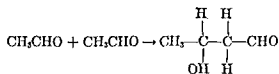
Carbohydrates and other polyhydric aldehydes, which are of vital importance biologically, may form from aldehydes in this manner.

UNSATURATED ALDEHYDES

Aldehydes possessing unsaturated linkages in their structures are known but are of no importance in anesthesia. Acrolein or propenal is the simplest member

of the *unsaturated* aliphatic series of aldehydes. Structurally, it is ethylene with one hydrogen atom replaced by the aldehyde group:

$$CH_2\!\!=\!\!\overset{\overset{\displaystyle H}{|}}{C}-CHO$$
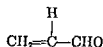
Acrolein is an irritating substance which possesses a bronchoconstrictor action. Small amounts form when glycerol is oxidized at high temperature in the presence of a dehydrating agent, or when fats burn.

The names of aldehydes usually end with the suffix "al." Formaldehyde may be called methanal; acetaldehyde; ethanal, propionaldehyde, propanal, butyraldehyde, butanal, and so on.

KETONES

Ketones may serve as starting products for some anesthetic drugs. Ketones, themselves, are not used for anesthesia. The simplest member of the aliphatic series of ketones, dimethyl ketone, is known as acetone. Acetone possesses a symmetrical structure:

$$CH_3-\overset{\overset{\displaystyle }{}}{\underset{\underset{\displaystyle O}{\|}}{C}}-CH_3$$

In symmetrical ketones, both radicals attached to the carbonyl or ketonic group are similar. In unsymmetrical ketones, the radicals are dissimilar. The ketonic group, as with the aldehyde group, may occur on aromatic, alicyclic, and heterocyclic structures also.

Phenyl methyl ketone,

or "hypnone," is one of the few ketones which has been used clinically: Ketones,

like aldehydes, are water-soluble substances. Usually they are liquids. Some are solids, depending upon their molecular weight. The low molecular weight ketones are flammable. An increase in molecular weight, as with other compounds, results in a decreased volatility, water solubility, and flammability. Ketones behave in many ways like aldehydes. Reduction by hydrogen, aided by a catalyst, forms the secondary alcohol from which it is originally derived. Dihydric alcohols, knowns as *pinocals*, also form during the reduction. Oxidation of ketones with mild agents, such as silver or copper reagents, used to oxidize aldehydes, is not easily accomplished. Vigorous oxidation causes a breakdown of the molecule to acids, aldehydes, and other miscellaneous products. Ammonia, hydrogen cyanide, hydroxylamine, and hydrazines react with ketones in the same manner as do aldehydes. Sodium bisulphite adds to ketones, but only to alkyl methyl ketones:

$$CH_3-\overset{\overset{\displaystyle ONa}{|}}{\underset{\underset{\displaystyle HSO_3}{|}}{C}}-R.$$

Ketones do not polymerize easily. The names of *ketones usually end with the suffix "one."* Thus, acetone may also be called propanone; methyl ethyl ketone, may be called butanone, and so on up the aliphatic series. Unsaturated ketones are known but are not important in this discussion.

Ketones manifest *tautomerism* (Chap. 9). Certain atoms of certain types of compounds are able to "wander" or shift from one position to another in the molecules to form new isometric structures. Such a shifting is called tautomerism. The isomers are *tautomers*. In the case of ketones, a hydrogen atom migrates

from the adjacent carbon to the carbonyl to form an *"enol"* instead of a ketone. The hydrogen of the hydroxyl group of the enol can often be substituted by metals. The reaction of ketone to enol is reversible. This phenomenon occurs in barbiturates also (Chap. 19).

Aldehydes and ketones react with halogens and phosphalides to form a variety of useful derivatives. Halogenated ketones are starting points for hypnotic and anesthetic drugs. These are described in detail under halogenated compounds. Halogenated ketones possess irritating (tear gases) properties and are, therefore, of little use as hypnotics. In fact some have been used as gases for warfare.

PARALDEHYDE

FORMATION

Paraldehyde forms by the polymerization of three molecules of acetaldehyde in the presence of a trace of concentrated sulphuric acid. Heat is evolved in the reaction. Paraldehyde possesses a cyclic structure consisting of alternate oxygen and carbon atoms (page 277).

The substance is a mild hypnotic of low potency, introduced into medicine by Cervello in 1882. The molecule possesses no free aldehyde group and, therefore, does not respond to any of the chemical tests for aldehydes. Therefore, sodium bisulphite, ammonia and hydrogen cyanide do not form addition compounds. No reduction occurs with copper and silver reagents.

PROPERTIES

The polymer is a colorless liquid with a characteristic, pungent, somewhat fruity odor, and a warm but disagreeable taste. As one would expect from its specific gravity (0.994 at 25°C.), the liquid overlays water. It boils at 124°C. The

index of refraction, using a sodium light at 20°C., is 1.4049. Paraldehyde is moderately soluble in water—1 in 8 parts at 25°C. The solubility decreases as the temperature rises (1 in 17 at 100°C.). The drug is highly soluble in organic solvents, such as ether, chloroform, alcohol, and oils. The oil/water distribution coefficient at 37.5°C. is 3.87. The ratio is low because the drug has both a moderate degree of water solubility and a high lipoid solubility.

STABILITY AND REACTIVITY

Paraldehyde decomposes if exposed to light, acids, and air. Dark, well-stoppered bottles are used for storing the drug. The most common impurity in paraldehyde is acetaldehyde which results from depolymerization. Acetaldehyde may be detected by the use of Tollen's reagent which yields a black precipitate in the presence of the free aldehyde group. If a portion is treated with dilute potassium hydroxide, a yellow color forms if free aldehydes are present, due to the formation of resins.

Aldehydes are easily oxidized to acids. Aqueous solutions of pure paraldehyde are neutral. Sulphates and sulphuric acid, which could be contaminants of manufacture are detected by means of barium salts. One drop of hydrochloric acid and three drops of saturated barium chloride solution are added to 10 cc. of a 1 in 10 aqueous solution of paraldehyde in distilled water. A white precipitate of barium sulphate forms if the test is positive. Chlorides, or hydrochloric acid, are detected by adding several drops of concentrated silver nitrate acidified with concentrated nitric acid to dilute aqueous solutions of paraldehyde. A white precipitate indicates the presence of a halide ion. Aldehydes are estimated quantitatively by titrating with solutions of hydroxylamine hydrochloride.

QUANTITATIVE ANALYSIS

Methods have been devised for quantitative estimation of paraldehyde in blood and other fluids. The paraldehyde may be depolymerized with sulphuric acid and the acetaldehyde isolated by steam distillation into a measured excess of sodium bisulphite. The aldehyde combines to form a bisulphite addition product. The uncombined sodium bisulphite is titrated with iodine. The aldehyde bisulphite addition product is then decomposed by means of sodium carbonate and the liberated sodium bisulphite is titrated with standard iodine solution. Computation of the quantity of aldehyde is made from this latter titration. Bodansky and his associates oxidized the acetaldehyde to acetic acid with a potassium dichromate and sulphuric acid mixture instead of combining it with sodium bisulphite. A known excess of chromic acid mixture is employed. The aldehyde content is calculated from the unused portion of chromate mixture, which is determined iodometrically.

Paraldehyde has a low vapor pressure at room temperature and cannot be administered by inhalation. It is, therefore, classed among the non-volatile compounds. The concentration in blood of dogs anesthetized with the drug averages 80 mgm. per 100 cc. The drug is distributed throughout all tissues. Muscles, liver, and spleen absorb the drug in approximately equal amounts.

DETOXIFICATION

The metabolic fate of paraldehyde is not definitely known. Apparently it

varies from species to species. A certain amount is eliminated unchanged by the lung in man and can be detected in the exhaled air shortly after ingestion. Defandorf noted that 7% of the total paraldehyde administered to dogs by vein to produce anesthesia was eliminated within 24 hours. A product is eliminated in the urine of dogs which has reducing properties. Detoxification in the dog is by conjugation. The liver plays the important role in detoxification. In the rat, paraldehyde is eliminated practically unchanged quantitatively. The exact metabolic fate in man remains to be determined. Some unchanged paraldehyde is eliminated in urine of man and animals.

FLAMMABILITY

Paraldehyde may be ignited by applying a flame directly to it or by heating it. It burns with a smoky flame. The vapor concentrations are so low at ordinary temperatures that air or oxygen mixtures are non-explosive.

The drug is compatible with benzyl alcohol. The latter is an aromatic alcohol used for local anesthesia to alleviate irritating effects produced by paraldehyde upon the mucosa following rectal use.

Acids, Acyl Derivatives, and Esters

ACIDS

MONOCARBOXYLIC ACIDS

THE *carboxyl* group,

$$-\overset{\overset{\text{O}}{\|}}{\text{C}}-\text{OH},$$

is a radical composed of a carbonyl group, $C = O$ and a hydroxyl group. The carboxyl group, often written (COOH), confers acidic properties to organic compounds. One carboxyl group replaces one hydrogen atom of a compound to form a *monocarboxylic* acid. The carboxyl group combines with hydrogen to form the simplest organic acid, formic acid. In the series of saturated straight-chain hydrocarbons, such a substitution on a terminal carbon atom gives rise to a series of aliphatic monocarboxylic acids often referred to as the *fatty acids*. The acid which forms when one hydrogen of methane is substituted is called acetic acid and is represented by the structure CH_3COOH. Propionic acid, the next higher member of this aliphatic series, is C_2H_5COOH; butyric is C_3H_7COOH; valeric is C_4H_9COOH; and so on. The high molecular weight derivatives, those with 16, 18, and 20 carbon atoms, are known as *the fatty acids*. They are important in lipoids. Oxidation of aldehydes produces carboxylic acids.

POLYCARBOXYLIC ACIDS

When two carboxyl groups are substituted for hydrogen atoms on a compound, a *dicarboxylic* acid results. The simplest dicarboxylic acid is oxalic acid which consists of two carboxyl groups joined together

$$\begin{array}{c}\text{COOH}\\|\\\text{COOH}\end{array}$$

A *dicarboxylic acid of interest in anesthesia* is malonic acid. Malonic acid is important in the formation of barbiturates (Chap. 15). It is really acetic acid with one additional carboxyl group replacing a hydrogen atom $CH_2(COOH)_2$. Other important dicarboxylic acids are succinic, tartaric, glutaric, maleic, and fumaric.

Acids may be unsaturated and contain double bonds. Oleic acid, $C_{17}H_{33}COOH$, the most familiar of this type, is an important constituent of fats and oils. The straight-chain aliphatic, monocarboxylic acids, both saturated and unsaturated, are called *fatty acids*. Tricarboxylic acids are also known, of which citric acid is the most important.

When the carboxyl group replaces one or more hydrogen atoms on the benzine ring and other aromatic hydrocarbons, *aromatic acids* form. One hydrogen on the benzine ring replaced by a carboxyl group forms benzoic acid,

Similar substitutions on the naphthalene hydrocarbon give rise to naphthoic acid,
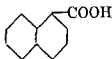
Heterocyclic groups and alicyclic compounds may also have the carboxyl group substituted on their structures to form acids.

The replacement of a hydrogen atom of a hydrocarbon by a carboxyl group markedly decreases its volatility and flammability and increases its water solubility. *The lipoid solubility may diminish.*

In aqueous solution, organic acids ionize to yield hydrogen ion as do the mineral acids. The hydrogen ion is represented as coming from the hydroxyl of the carboxyl group:

$$\underset{\underset{R-C-OH}{\|}}{O} \rightarrow \left[\underset{\underset{R-C-O}{\|}}{O}\right] + H^+ .$$
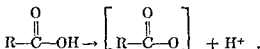
Certain substances, of which barbituric acids are perhaps the best examples, do *not have a carboxyl group but do behave* as acids. These will be discussed subsequently. Neutralization of organic acids by mineral or organic bases yields *organic salts.* The metallic ion replaces the hydrogen in the hydroxyl of the carboxyl group:

$$CH_3COOH + NaOH \rightarrow CH_3COONa + H_2O$$
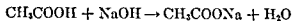
Organic acids react with alcohols to form *esters* and water:

$$RCOOH + R_1OH \rightarrow RCOOR_1 + H_2O$$
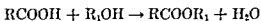
HYPNOTIC EFFECTS OF ACIDS

Carboxylic acids are unimportant as anesthetic drugs. As a rule, if a carboxyl group enters into the structure of a compound which possesses anesthetic activity, this activity decreases or is entirely suppressed. Ethylene, which is a hydrocarbon and is a satisfactory anesthetic *drug*, forms acrylic acid when one hydrogen atom is replaced by a carboxyl group:

$$CH_2\text{=}CH_2 \rightarrow CH_2\text{=}CH\ COOH$$

The acid thus formed is an irritating non-anesthetic substance. In the cocaine molecule, methyl ecgonine is essential for anesthetic activity. If hydrolyzed to ecgonine and methyl alcohol, a free carboxyl group is present on the molecule and the anesthetic property of the substance is decreased.

NOMENCLATURE

Carboxylic acids are designated by the ending "*oic*" which replaces the "e" of the hydrocarbon. Formic acid may be called methanoic acid; acetic, ethanoic; propionic, propanoic; butyric, butanoic; and valeric, pentanoic and so on up the series.

ACYL COMPOUNDS

The radical,

$$\underset{\underset{CH_3-C-,}{\|}}{O}$$

is called the *acyl* radical. The acyl radical is derived from a carboxylic acid by dropping the OH group. Acids could be considered as "acyl hydroxides." The

acyl group may enter into many organic compounds. The acyl radical is named after the acid from which it is derived. The acyl chloride of acetic acid is called *acetyl chloride.* The "ic" of the ending of the acid is substituted by "*yl.*" Acyl oxides are anhydrides of organic acids. Diacetyl oxide, or acetic anhydride,

CH₃—C
‖
O
\
O
/
CH₃—C
‖
O
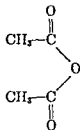
yields acetic acid when mixed with water. Certain compounds derived by acylation of ammonia, known as amides, are important as hypnotic drugs. These will be described subsequently.

ESTERS

Alcohols, and this applies to all types, primary, secondary, tertiary, aliphatic, aromatic, alicyclic, or heterocyclic, react with mineral or carboxylic acids to form *esters*. The hydrogen of the acid and the hydroxyl group of the alcohol unite to form water. The acid radical joins with that of the alcohol forming an ester. The reaction between ethyl alcohol and acetic acid to form ethyl acetate is illustrated by the following equation:

$$CH_3COOH + C_2H_5OH \rightarrow CH_3COOC_2H_5 + H_2O$$
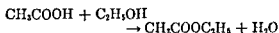
Ethyl acetate is a clear, colorless, flammable liquid which boils at 77°C. It possesses a characteristic fruity odor and pleasant taste. Ethyl acetate possesses some narcotic potency but less than ethyl alcohol, yet, of course, more than acetic acid which has none. Esters of aliphatic acids and alcohols are unimportant as anesthetics or sedative drugs because they are weak depressants. Certain heterocyclic and aromatic esters are of considerable importance as local anesthetic drugs or stimulants. Certain esters of carbamic acid and aliphatic alcohols have been used for sedation. Inasmuch as carbamic acid is a relative of urea, these are discussed under that heading.

If esters react with water in the presence of acids or alkalies, they undergo *hydrolysis*. The hydrogen and the hydroxyl ions of water are utilized to regenerate the acids and the alcohol.

Ethers, Alkene Oxides, and Acetals

GENERAL CONSIDERATION OF ETHERS

ETHERS ARE *organic oxides.* Two organic radicals are attached to an atom of oxygen. They may be considered as water, which is hydrogen oxide (HOH), with both its hydrogen atoms substituted by alkyl, aryl, alicyclic, or heterocyclic groups (R—O—R). The alkyl substitutions yield aliphatic ethers which are of importance because they possess anesthetic properties. The alkyl radicals are derived from alcohols. Ethers may be either *symmetrical,* where the same group is used to replace both hydrogen atoms of water, or *unsymmetrical,* where the groups are dissimilar. In cases where one or both substitutions are aryl groups, aromatic ethers form. Generally if one group is an alkyl and the other an aromatic or other type grouping the ether is still considered as being aromatic. Aromatic ethers are unimportant as general anesthetic drugs since they have no anesthetic activity. Alicyclic and heterocyclic ethers are also known. Mixed alicyclic and aliphatic ethers posses anesthetic properties. Unsaturated ethers also exist. The radicals may be arranged so that one is saturated and one unsaturated, or the ether may be symmetrically unsaturated.

ALIPHATIC ETHERS

Aliphatic ethers may be straight chained or the chain may be branched. The hydrogen atoms may be replaced by halogens to give halo ethers or by hydroxly groups to form hydroxy-ethers. The simplest member of the series of saturated aliphatic ethers is dimethyl ether. CH_3—O—CH_3. Richardson attempted to introduce this as an anesthetic agent in 1867 but the results of its use are disappointing. The ether is a gas which boils at $-23°C$. and requires an inhaled concentration of 60% to 80% by volume for anesthesia in animals. Methyl ethyl ether, CH_3—O—C_2H_5, boils at 7.9°C. No mention of its use as an anesthetic is made. The next member of the series is diethyl ether, or the "ether" which is so widely used in medicine. Diethyl ether boils at 34.6°C. and requires an average of 4% in the alveoli for anesthesia. Methyl propyl ether (Metopryl) is an isomer of ethyl ether. It is more potent. Brown used n-propyl ethyl ether, C_3H_7—O—C_2H_5, which boils at 63.6°C. and found the drug potent and safe in man. This ether seems to be more potent than ethyl ether.

The greater narcotic potency of unsaturated hydrocarbons, such as ethylene and propylene, over the saturated counterparts attracted attention to unsaturated ethers. A series of unsaturated ethers was investigated by Leake and Chen. These included divinyl oxide, ethyl vinyl oxide, and allyl ethyl oxide. Divinyl oxide was found to possess the least toxicity and to be the most useful of the lower molecu-

lar weight unsaturated ethers. The potency of these unsaturated compounds is greater than that of the saturated but the demarcation is not as well defined as between saturated and unsaturated hydrocarbons. The success of the cyclic hydrocarbon, cyclopropane, directed Krantz and coworkers to investigate the potency and usefulness of alicyclic substituted ethers. The simplest member of the series of alicyclic ethers is cyclopropyl methyl ether (cyprome). This ether is more potent than the straight-chain isomer. The next higher homologue is cyclopropyl ethyl ether (cypreth). This possesses anesthetic potency greater than the lower molecular weight homologue. It has been under investigation as an anesthetic for man. Cyclopropyl propyl ether and cyclopropyl butyl ether have been prepared and are also under investigation. Recently, cyclopropyl vinyl ether has been prepared with the idea of combining radicals derived from cyclopropane, divinyl ether, and the oxy group of ethers—all potent agents.

POTENCY AND STRUCTURE

Ethers are prepared from alcohols or other derivatives of alcohols. Methyl ethyl ether, for example, is derived from and related to methyl and ethyl alcohols. Ethers are more volatile than the corresponding alcohols from which they are derived. Ethyl alcohol, from which ethyl ether is derived, boils at 78°C. However, the ether is less volatile than the hydrocarbon to which the alcohol is related. Dimethyl ether, for example, although a vapor, boils at a higher temperature than methane. Volatility of an ether decreases with the increase in carbon content or molecular weight of the ether. Water solubility of ethers is low and always less than that of related alcohols. Water solubility is greater than the hydrocarbon to which the ether is related. Water solubility decreases with molecular weight. Aliphatic and alicyclic ethers are lipophilic. Potency and toxicity of ethers increases as the molecular weight increases. For example, dimethyl ether is less potent than diethyl, and diethyl ether is less potent than methyl propyl ether. In the series of symmetrical aliphatic ethers, of 2–10 carbon atom content, the potency varies inversely as the volatility. Of two isomeric ethers the ether with the longest chain is the most potent. Likewise the one with the highest boiling point is the most potent. Hydroxylation of an aliphatic ether reduces its narcotic potency. Dihydroxy diethyl ether (diethylene glycol) is more water soluble than ethyl ether, but lipophilic properties are lost. Halogenation decreases volatility and increases potency, irritating and toxic properties. Halogenated ethers are discussed in Chapter 15.

Unsaturated ethers are more volatile and generally less stable than saturated ethers. Polymerization occurs more readily than with saturated compounds. Toxicity of aliphatic ethers increases directly as molecular weight increases irrespective of isomeric structure. Ethers prepared from branched-chain alcohols are more volatile than those from straight-chain compounds. Water solubility decreases as molecular weight increases since the compound tends to approach the hydrocarbons in physical and chemical properties.

FLAMMABILITY

Ethers are flammable. The flammability decreases as the molecular weight increases. The lower limit of flammability in volumes per cent of aliphatic satu-

rated ethers is, roughly speaking, the number of carbon atoms in the ether divided by six. Force of explosion is less if the mixture is composed of higher molecular weight ethers.

Ethers are inert to many chemical agents in vitro. A cleavage occurs at the oxygen linkage which regenerates the alcohol. If an ether reacts with concentrated cold hydriodic acid or warm concentrated sulphuric acid, or is treated with steam under pressure, an alkyl halide or bisulphate forms in addition to the alcohol. The following equations illustrate the reaction. A single cleavage results with these reagents—that is, only one alkyl radical is detached from the oxygen atom.

$$R—O—R + H_2SO_4 \rightarrow ROH + RHSO_4 \text{ (sulphuric acid)}$$
$$R—O—R + HI \rightarrow ROH + RI \text{ (hydriodic acid)}$$
$$R—O—R + H_2O \rightarrow ROH + ROH \text{ (steam)}$$
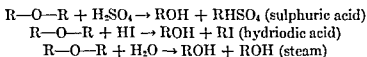
Reagents, such as phosphorus pentachloride, hot hydriodic acid, and hot concentrated sulphuric acid cause a double cleavage at the oxygen linkage. Both alkyl radicals are detached from the oxygen atom:

$$R_1—O—R + PCl_5 \rightarrow R_1Cl + RCl + POCl_3$$

$$R_1—O—R + 2HI \rightarrow R_1I + RI + H_2O$$
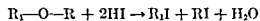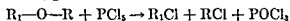
Hydrogen atoms in the aliphatic or aromatic radicals may be replaced by halogens and other substituting groups. All the hydrogen atoms may be replaced by halogens so that there is a complete substitution on the radical. Prior to the introduction of fluorinated ethers halogenated ethers were not considered to be important.

Oxidation converts ethers to peroxides. Their general formula may be described as being $[R—O—R)_2O_2]_n$. Ether peroxides are unstable substances. Their exact chemical structure is undetermined and may vary with the type of ether and conditions under which oxidation occurs. Other chemical reactions are discussed in detail under individual ethers. Ethers may be named by the Geneva system. Dimethyl ether would then be called methoxymethane; ethyl ether, ethoxy ethane and so on. As a rule, volatile anesthetic ethers of the aliphatic and alicyclic type all appear to be inert in the body and are eliminated unchanged.

ETHYL ETHER

HISTORY

The ethyl radical, or structures related to it, seems in many cases to be the least toxic and most satisfactory from a physiological standpoint. Ethyl alcohol is the initial raw material for many useful anesthetic drugs. In others, the ethyl radical enters into the structure or predominates as a substituting group.

Ethyl ether, the ordinary anesthetic "ether," has now had over a one hundred year-trial and still leads in satisfactory performance as an anesthetic agent. As has been previously mentioned, ethyl ether, or diethyl oxide, $C_2H_5—O—C_2H_5$, consists of two ethyl groups attached to an oxygen atom. Ethyl ether may also be called ethoxyethane. Ethyl ether was first prepared in 1540 by Valerius Cordus who referred to it as sweet vitriol. The narcotizing action of this important substance was first noted by Faraday. Ether was first used clinically for surgical anesthesia by Long of Georgia, in 1842, and Morton of Boston, in 1846.

sodium, however. Ether is unaffected by alkalies, either strong or weak, in dilute or concentrated solution. Concentrated sulphuric acid and potassium dichromate (chromic acid) first convert ether to alcohol and then oxidize it to acetic aldehyde. Acetic acid and—ultimately—water and carbon dioxide form if heated. This reaction is used as the basis for quantitative analysis. Ethers readily react with concentrated hydrogen iodide (HI) to form an organic iodide and the alcohol. This reaction is of extreme importance in the identification of oxy linkages in organic compounds. Hydriodic acid and the ether interact to form ethyl iodide and ethyl alcohol. The reaction readily occurs even at room temperatures. Ether combines with bromine at low temperatures to form an addition product, $(C_2H_5)_2O \cdot Br_2$, which is a solid melting at $-24°C$. When warmed, this compound decomposes into its original products. Bromine and other halogens at room temperature substitute for the hydrogen on the ethyl groups to form halo ethers. The hydrogen nearest the oxygen reacts first:

which oxygen is believed to have a valence of 4. This comes about through the action of two unshared electrons in the oxygen atom of the ether. These substances, called oxonium compounds, are unstable. Those formed by hydrogen chloride are represented by this structure:

$$R_1\text{---}O\text{---}R + HCl \rightarrow \begin{array}{c} R_1 \quad Cl \\ O \\ R \quad H \end{array}$$
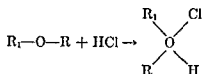
Ether is not oxidized by either acid or neutral solutions of potassium permanganate.

STABILITY AND PURITY

The purity of ether is of utmost concern to the anesthesiologist. Impurities in anesthetic ether may originate from three sources: contamination during manufacture, deterioration during storage, or decomposition or contamination during clinical use. Contaminants of manufacture, such as thioacids, sulphur oxides, thioethers, sulphates, ethylene, aldehydes, and organic acids occur in-

$$(C_2H_5)_2O + 2Cl_2 \rightarrow H_3C\text{---}\underset{\underset{Cl}{|}}{\overset{\overset{H}{|}}{C}}\text{---}O\text{---}\underset{\underset{Cl}{|}}{\overset{\overset{H}{|}}{C}}\text{---}CH_3 + 2HCl$$
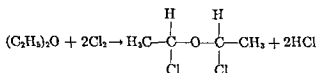
The others are substituted in turn until all the hydrogen atoms are replaced. Chlorine forms with a compound, perchloroether, $(C_2Cl_5)_2O$, which is a solid with a camphor-like odor. Ethyl ether does not react with acetyl chloride, organic acids, or the trihalide of phosphorous, PCl_3. The pentahalide, PCl_5, reacts with ether to form a variety of halogenated compounds, depending upon the temperature of the reacting mixture. The hydrogen halides form compounds in

frequently with present day methods of manufacture and purification. Although methods of packing and storage have improved, oxygen and water vapor are difficult to exclude. These, together with the alcohol, which is also difficult to exclude, favor the formation of ether peroxides, acetaldehydes and other aldehydes and organic acids. Ether oxidizes slowly in the presence of oxygen to form ethyl and other *peroxides*. The exact structure of these peroxides is not known

because the substances are unstable and it is difficult to isolate them in pure form. The peroxides are probably polymers represented by the empiric formula $[(C_2H_5)_2O_2]_n$. Pure *ethyl peroxide explodes* when heated above 100°C. Sunlight and ultra-violet light favor the oxidation of ether and the formation of peroxides. Peroxides form slowly in ether packed in ordinary tin containers without precautions to inhibit oxidation. Their formation is slow, particularly if the containers are sealed and light-proof. Peroxides are probably the first impurities to develop in ether. Generally they form within six months after packing and persist for a year or more. Old ether contains less peroxide than new. Peroxides favor the formation of aldehydes. Aldehydes form while peroxides are disappearing, as a rule. The time of development of aldehydes and peroxides varies with the purity of the sample, type of container, conditions of storage, temperature, amount of oxygen, and moisture included when the container was sealed. Usually, aldehydes form after a period of six months after packing and persist for a year or more. Heat and light stimulate their formation. Much of the aldehyde present is acetaldehyde which forms from the oxidation of the alcohol in ether. Thus, alcohol, instead of acting as a preservative as it does when added to chloroform, favors the deterioration of ether. Storage in a dark, cool place retards oxidation. Contaminated ether has been observed to develop peroxides less readily than ether of high purity.

PRESERVATION OF ETHER

Numerous methods have been devised to prevent formation of impurities of ether for anesthesia during storage. Carbon dioxide has been added to replace oxygen but has not proved satisfactory. Certain metals, particularly iron, mercury, and copper, prevent the oxidation of ether since they are oxidized preferentially and consume all the available oxygen which is sealed with ether. Tin apparently does not prevent the formation of aldehydes and ketones because it resists oxidation. Copper-plated metal containers are commercially feasible. Copper inhibits oxidation even if ether is exposed to temperatures over its boiling point in the presence of oxygen. Ether exposed to heat and pressure may develop appreciable quantities of peroxides within an hour. Only a very thin layer or plating of copper is required to retard oxidation. Iron wire placed in containers has been used to inhibit oxidation. However, the rust which forms discolors the ether and is, therefore, objectionable from the sake of appearance even though it does not detract from its value. Once peroxides, aldehydes, or other impurities have formed, the subsequent addition of copper or any inhibiting agent has no effect upon them.

Impurities which form after the ether container has been opened vary in composition. Ether is usually vaporized by passing oxygen or air through the pure liquid. Small amounts of peroxides and aldehydes may form in this process. Heat is often used to assist in the vaporization. This greatly increases the rate of oxidation. Ether vaporizers are usually equipped with clear glass jars. The accelerating effect of light upon oxidation has been repeatedly demonstrated. Contamination by impurities from use of unclean equipment may also assist in the formation of additional undesirable products.

The length of time ether may be kept and used from an opened container de-

pends upon the type of container. The ether remains stable for days if the container is plated with copper or some alloy containing copper. Hediger and Gold showed that ether from large containers is satisfactory even though exposed to air for as long as sixty-eight days. Ether ordinarily is packed in various sized containers, quarter-pound, half-pound, one pound and five pounds. Some anesthetists have, for reasons of economy, turned to the use of ether packed in bulk (27 and 55 pound drums). Even though the stability of this ether may be assured, the fire hazard from this practice must be considered. The National Fire Underwriters advise storage in a special, well ventilated room equipped with exhaust fans and spark proof electrical equipment and exercising of precautions to prevent discharges of static electricity. Perhaps the saving effected by this practice is offset by the inconvenience encountered.

Hazards of Impurities

Some doubt exists as to whether or not the impurities in ether are detrimental to man. Bourne found that concentrations of aldehydes up to 0.5% produced no significant effects in experimental animals. Mercaptans, up to 1%, peroxides up to 0.5%, and ethyl sulphide may cause gastric irritation but apparently no other particular deleterious effects. Various ketones—diethyl and methyl—cause no noticeable effect in concentrations up to 0.5%. Mendenhall and Connolly found ether containing aldehydes and peroxides more toxic to cilia of the respiratory tract than pure ether. Knoefel found impure ether produced anesthesia in mice more slowly than pure ether. Many other workers

have made similar observations. Regardless of whether or not impurities are safe or unsafe, one cannot be too cautious in the clinical administration of anesthetic drugs. All possible precautions should be observed to insure the safety of the patient.

Detection of Impurities

The noxious agents just mentioned may be easily detected by a number of simple tests with which every clinician who frequently employs the drug should be familiar. Ether should be neutral in reaction. If several ml. of ether are shaken with an equal portion of distilled water both layers should be neutral to litmus or other indicators. A number of tests for aldehydes have been devised. One simple test easily executed by the clinician is based upon the ability of aldehydes to reduce the mercuric complex in Nessler's solution: 20 ml. of ether are shaken with 3 ml. of this reagent and the two layers are allowed to form. A yellow color develops immediately in the aqueous layer. Large amounts of aldehydes produce a yellow precipitate. Upon standing, a precipitate or discoloration appears regardless of the aldehyde content. The alcohol in ether slowly oxidizes and reduces the mercuric salts. The presence of 0.0001% or more aldehyde is detected by this test. Peroxides may be detected qualitatively by shaking 10 ml. of ether with 1 ml. of 10% neutral potassium iodide and allowing the mixture to remain in a corked container in the dark for thirty minutes. A yellow color forms in the ether layer which indicates that elemental iodine has been liberated from the iodide by the peroxides. The addition of an aqueous solution of starch and the subsequent

formation of a blue color is confirmatory. As low a concentration as 0.0005% peroxide is detected by this test. The test may be read within five minutes, although it is recommended that an interval of thirty minutes be allowed to elapse before a final negative judgment is given.

QUANTITATIVE ESTIMATION

A number of tests have been devised for the quantitative estimation of ether. Ether may be determined in blood, body fluids and tissue, or gas ether vapor samples by means of the iodine pentoxide train (Chap. 7). The ether is oxidized by iodine pentoxide to carbon dioxide and water. The vapor is extracted by distillation from the fluid or tissue and drawn through the oxidizing tube by means of a current of air. The oxidation is accompanied by a corresponding reduction of the iodine pentoxide to free iodine. The latter is collected in aqueous potassium iodide solution and titrated using standard sodium thiosulphate solution. The reaction is quantitative and the amount of ether is calculated from the iodine liberated.

Nicloux, Ronzoni, Price and others have used the sulphuric acid-potassium dichromate method for the quantitative determination of ether. Ethyl alcohol forms first. Under carefully controlled conditions of concentration of acid chromate and temperature the alcohol is oxidized to aldehydes. The chromic acid is simultaneously reduced in proportion to the amount of ether oxidized. Larger samples are required for this type of determination than with the iodine pentoxide train. The alcohol is oxidized to acetaldehyde. However, the reaction may not stop at this point unless tem-

peratures and concentrations are carefully controlled and the aldehyde may be oxidized to acids. This would, of course, introduce an error in the determination. Ketones, alcohol, and other ethers may interfere with the test since they, too, are simultaneously oxidized. A known quantity of chromic acid is used in excess of that necessary to oxidize the ether. The chromic acid changes from yellow to green as it is reduced. The unchanged acid may be determined colorimetrically or by iodimetric titration.

Ether interferes with the determination of blood gases on the manometric apparatus of Van Slyke and Neill. Blood gases cannot be accurately determined in blood drawn from patients anesthetized with ether. The ether possesses a high vapor pressure at room temperature which interferes with the manometric readings. Besides, there is a difference in solubility of the extracted ether in each of the various reagents used for the absorption of gases which further adds to the inconsistent results. Shaw and coworkers devised a modification of the method whereby the ether is removed with glycerine in a Hempel pipette before the gas pressures are measured and absorption is attempted. Ether is also measured by the use of physical methods. Tarrow and his associates have employed the infra-red technique. The ether is first salted out of the blood with sodium hydrosulphate. Ether vapor behaves like a heteroatomic gas and absorbs radiation in the infra-red frequency range of the infra-red electromagnetic spectrum. The gas chromatograph (Chap. 7) also may be used to quantitate ether vapor in a mixture of several gases or vapors.

ELIMINATION

Ether is exhaled through the lungs entirely unchanged. There is no evidence that ether is chemically altered within the body. Upwards of 90% is eliminated by exhalation. The concentration in urine parallels the plasma concentration. The amount eliminated by the kidney, and through the skin and gastrointestinal tract is low, however. Ether possesses an air/blood distribution ratio of 1:15. Partly on this account, induction with the agent is slow. Desaturation is likewise slow, since with each circuit of venous blood from the tissues to the lungs, the partition between blood and alveolar air is only one part for alveolar air to the fifteen which remain in the blood. Ether conforms to the Overton-Meyer rule. At 37.5°C. the oil/water ratio is 3.2 and the oil/blood ratio is 3.3. Although ether has a great affinity for lipoids, the water organs (such as muscle, liver, and spleen) absorb considerable amounts also. This also accounts to a certain extent for the long induction and the long period of desaturation. The longer the administration of the anesthetic continues, the greater the amount absorbed and the longer will be the time interval for complete elimination (Chap. 4).

BLOOD LEVELS

There is no agreement in the values for the concentration of ether in the inspired air and blood required for surgical anesthesia. This is due to variations in responses between different subjects, variations in signs used to judge depth of anesthesia by individual workers and to differences in techniques of analysis. The usual figures for man range from 50 mgm. to 130 mgm. per 100 ml. of blood for second plane anesthesia. The inspired concentration for surgical anesthesia varies from 3.5% to 4.5% by volume. The lethal concentration in dogs is 6.7% to 8%. The lethal concentration in man is not known. The relatively low concentration required for anesthesia permits the use of air as the source of oxygen in inhaled mixtures since its presence only slightly reduces normal oxygen tension in such a mixture.

Ether is absorbed by the colon from mixtures of ether and mineral and vegetable oils. Ether absorbed in this manner is eliminated through the lungs, kidney, and skin in the same manner as if it were inhaled. Ether disappears rapidly from an isolated lung lobule with its blood supply intact—usually within two to three minutes (air disappears in 16 hours under similar conditions).

FLAMMABILITY

The range of flammability of ether is from 1.83% to 48.0% when mixed with air, and 2.10% to 82.5% with oxygen at 25°C. and atmospheric pressure. The anesthetic range (4%), therefore, lies within the flammable range. Nitrous oxide supports combustion of ether-air or ether-oxygen mixtures. A mixture of pure nitrous oxide and ether has a range of flammability ranging from 1.5% to 24.2%. The minimum ignition temperature of ether in air is 304°C.; in oxygen 359°C. The difference between oxygen and air is noteworthy. The inhaled concentration required for anesthesia is near the lower limit of flammability so that dilution may occur quickly to below the flammable range should the mixture leak or escape. The presence of peroxides in ether reduces the flash point of the ether since these are less stable. The ignition temperature may be less than 100°C., depending upon the type and

concentration. The flash point of pure ether is −45°C. (−49°F.).

METHYL PROPYL ETHER (METOPRYL)

Methyl propyl ether is an isomer of ethyl ether. It *was first studied by* J. C. Krantz in 1946. It was used clinically under the name of Metopryl. The ether *resembles ethyl ether in odor and general characteristics.* The boiling point is 38.8°C. The specific gravity is 0.726 at 16°C. The oil/water ratio at 20°C. is 10. It is somewhat more potent than ethyl ether. It is chemically stable in the body. The general in vitro reactions are similar to ethyl ether. The ranges of flammability are close to those of ethyl ether. The drug was received unenthusiastically by clinicians because it had little to offer over ethyl ether. It is seldom used.

ISOPROPYL METHYL ETHER

Isopropyl methyl ether is an aliphatic ether which, like Metopryl, is an isomer *of ethyl ether. It was also studied by* J. C. Krantz. It is approximately 25% less potent than ethyl ether. Induction and *recovery are more rapid than with ethyl ether.* The oil/water ratio is 2 at 37°C. The compound had little to offer over ethyl ether.

ETHYL n-PROPYL ETHER

Ethyl n-propyl ether (C_2H_5—O—C_3H_7) *is the next higher homologue ether in the* series of homologous saturated aliphatic ethers. It is an unsymmetrical ether. In 1940 Brown introduced the ether as an anesthetic. The ether is prepared by the Williamson synthesis by refluxing sodium propylate with ethyl iodide.

odor is somewhat similar to that of ethyl ether. Its specific gravity is 0.750 at 25°C. Copper is used as a stabilizer as with ethyl ether. The potency is one and one-half to two times as great as that of ethyl ether. A concentration of 2.5% to 3% produces surgical anesthesia; 4% to 5%, respiratory failure. The ether is somewhat more potent than ethyl ether. The pharmacological properties differ little from those of ethyl ether. The ether is more difficult to volatilize than ethyl ether.

VINYL ETHER

HISTORY

Vinyl ether, or divinyl oxide, is a symmetrically unsaturated aliphatic ether *derived from vinyl alcohol.* Both *vinyl* alcohol and vinyl ether are related to the unsaturated hydrocarbon, ethylene. Vinyl alcohol (CH_2=CHOH) *is* the simplest member of the series of unsaturated straight-chain alcohols. The alcohol has never been prepared since molecular rearrangement occurs and the isomer, acetaldehyde, is formed when its synthesis is attempted. Vinyl halides are stable, however. The anesthetic properties of divinyl ether were first recorded by Leake and Chen in 1930. These workers examined a series of unsaturated ethers, among which were vinyl ethyl ether and allyl ethyl ether. They were prompted in their search by the success and use of ethylene as an anesthetic. Divinyl ether, the lowest *member of the unsaturated homologous* series of ethers, was found to be the most potent and the least toxic of the group. Semmler first described a substance

$$C_2H_5I + C_3H_7O—Na \rightarrow C_2H_5—O—C_3H_7 + NaI.$$

Ethyl n-propyl ether is a colorless, mobile liquid boiling at 63.6°C. The

which he believed to be divinyl ether *in* 1887 and which he prepared from vinyl

sulphide and silver oxide. Ruigh and
Major, in 1931, were unable to obtain
divinyl ether from divinyl sulphide and
silver oxide. Semmler's product boiled
at 39°C. Synthetic vinyl ether, prepared
by Ruigh and Major, boils at 28.3°C.
Ether is sometimes referred to as a
hybrid of ethylene and diethyl ether.

PREPARATION

Divinyl ether cannot be prepared from
its parent alcohol, as can ethyl ether. The
usual synthesis is to first chlorinate di-
ethyl ether to prepare β β' dichlorethyl
ether. The halo ether, is then fused with
molten potassium hydroxide to which
ammonia is added as a catalyst. A hy-
drogen atom and a chlorine atom are re-
moved from each ethyl radical forming
the unsaturated linkages:

parts dissolve in 100 parts of water; at
37°C., 5.25 parts dissolve. Ethyl ether is
more soluble in water than vinyl ether.
At 37°C. the oil/water distribution co-
efficient is 41.3. This value is much
higher than that of ethyl ether. Vinyl
ether is a lipophilic anesthetic and re-
sembles the hydrocarbon gases in its
pharmacologic properties.

STABILITY

Vinyl ether is not as stable as diethyl
ether due to the presence of unsaturated
linkages. In the presence of air or oxygen
formaldehyde, formic and acetic acids,
and complex peroxides form. Acids, even
in minute traces, hasten its deterioration.
Alkalies tend to stabilize it. Vinyl ether,
as is the case with other vinyl com-
pounds, polymerizes to form polyvinyl

$$\underset{\overset{|}{H}}{\overset{\overset{Cl}{|}}{H}}{-}\underset{\overset{|}{H}}{\overset{\overset{H}{|}}{C}}{-}O{-}\underset{\overset{|}{H}}{\overset{\overset{H}{|}}{C}}{-}\underset{\overset{|}{H}}{\overset{\overset{Cl}{|}}{C}}{-}H + \xrightarrow{\;2KOH\;} H{-}\underset{\overset{|}{H}}{\overset{\overset{H}{|}}{C}}{=}\underset{}{\overset{}{C}}{-}O{-}\underset{\overset{|}{H}}{\overset{\overset{H}{|}}{C}}{=}\underset{}{\overset{}{C}}{-}H + 2KCl + 2H_2O.$$

Various side reactions reduce the yield
and favor the production of impurities.
The contaminants of manufacture in-
clude hydrogen, acetylene, ethylene,
chloro-ethyl-vinyl ethers, aldehydes and
dioxane. Some acetic aldehyde forms as
a side reaction.

PROPERTIES

Divinyl oxide is a colorless, mobile
liquid which boils at 28.3°C. The drug
possesses an ethereal sweet odor. The
vapor is not irritating. The molecular
weight is 70. The specific gravity of the
liquid is 0.77 at 20°C., that of the vapor
is 2.2 (air = 1). The presence of the
double bonds causes the compound to
have greater volatility than its saturated
counterpart, ethyl ether. At 20°C., 4

resins. The resins often harden to glass-
like masses. A nonvolatile organic base,
phenyl-alpha-naphthylamine (0.01%), is
added as an alkalizer and stabilizer. Ab-
solute alcohol (3.5%) is added to decrease
the volatility and inhibit freezing of the
water vapor in the exhaled air on the
mask. Temperatures below 0°C. develop.
The latent heat of vaporization is 89
calories per gram at its boiling point.
The vapor pressure at 20°C. is 550 mm.
Hg. This mixture is known by the pro-
prietary name of "Vinethene" (Merck).
It is packed in amber-colored bottles
equipped with a special dropper for ad-
ministration by open techniques. The
addition of the stabilizer confers a pur-
plish fluorescence to the liquid which is
not seen with the pure oxide originally.

The manufacturers did not recommend the use of the drug after one year from the date of preparation. This time interval has recently been extended to two years. Likewise, they recommended discarding the drug twenty-four hours after opening the container. Adriani has shown that specimens are free from peroxides, aldehydes, acetylides, and resins for at least ten days after opening the container and using a portion of it if the remainder is well-stoppered and stored in a cool place.

"Vinethene" is stable in the presence of soda lime in carbon dioxide filters even though the mass is heated to as high as 70°C. from the reaction of absorption. Passing a stream of oxygen, air, or nitrous oxide through the agent to aid in vaporization causes no appreciable quantities of peroxide or aldehyde to form.

Vinyl ether containing aldehydes and peroxides is no more toxic than pure specimens in experimental animals. Induction time is considerably prolonged, however.

Distribution and Stability in Tissues

Divinyl ether is more potent than ethyl ether in regards to ability to cause unconsciousness. The inspired concentration averages 4%. The blood concentration required to maintain surgical anesthesia is less than that of ethyl ether, 30 mgm. to 40 mgm. per 100 ml. As far as it is known, vinyl ether is eliminated unchanged by the lungs. No evidence exists that it is polymerized in the body or altered chemically by tissues. The elimination is rapid. Rapid elimination is favored by its low blood solubility. Elimination is similar to that of cyclopropane. Recovery occurs in several minutes, but complete body desaturation is extremely slow and several hours may elapse before the lipoid tissues are totally free of the drug.

Reactivity

Vinyl ether undergoes certain chemical reactions which are due largely to the presence of the double bond. The ether is converted to ethyl ether by hydrogenation in the presence of platinum black which acts as a catalyst. The yield is less than 15%. Halogens, such as bromine and chlorine, readily add to the double bonds to form saturated halogenated ethers. Permanganate solutions are quickly discolored by the ether since the ether is oxidized to various aldehydes, ketones, and acids depending upon the temperature.

Detection of Impurities

Impurities may readily be detected by certain tests. Pure divinyl oxide shaken with water should be neutral. An aqueous solution of Vinethene is alkaline in reaction since the stabilizer is an alkaline substance.

A slight residue remains when a portion of Vinethene is evaporated to dryness since the stabilizer is nonvolatile. Aldehydes may be detected by using ammonium silver nitrate solutions, as described (see aldehydes). Acetylenes form precipitates (acetylides) with a reagent composed of ferric chloride, cobaltic chloride, and copper sulphate added to an aqueous solution of the ether.

Quantitative Determination

Vinyl ether may be determined quantitatively with the iodine pentoxide train. The vinyl ether is distilled from the tissues and drawn through the heated iodine pentoxide in the same

manner as with other ethers and alcohols. Carbon dioxide, free iodine, and water form. The titration and computations are similar to those for ethyl ether.

FLAMMABILITY

Vinyl ether is flammable. Mixtures of the vapor and air explode in concentrations ranging from 1.87% to 27.0% in air; 1.85% to 85.5% in oxygen and 1.4% to 24.8% in nitrous oxide at 25°C. and atmospheric pressure. The ignition temperature of vinyl ether is 353°C. in air and 313°C. in oxygen. The flash point is below 0°C.

ETHYL VINYL ETHER

HISTORY

The anesthetic properties of ethyl vinyl ether were first noted in mice by Leake and Chen in their study of vinyl and related unsaturated ethers in 1930. They, however, did not find the drug to be as effective as divinyl ether. Krantz and his co-workers felt that the compound warranted further study, and in 1942, undertook such studies in dogs and monkeys. They were impressed by the anesthetic potency and the wide therapeutic index of the drug. In 1951 several investigators initiated studies in man.

PREPARATION

Ethyl vinyl ether is a clear, colorless, volatile liquid. It is prepared by reacting acetylene with ethyl alcohol under pressure in the presence of potassium ethylate as a catalyst:

haled moisture on the mask in open techniques. Phenyl alpha naphthylamine (0.01%) is added to prevent oxidation and polymerization. Aldehydes, various oxides and resins form in the presence of acids or absence of stabilizers. Likely impurities are formaldehyde, formic acid, acetaldehyde and dioxane. It may be stored for periods of a year in dark containers unopened with the stabilizer.

PROPERTIES

The ether is a clear, colorless liquid which possesses a faint purple fluorescence when viewed through transmitted light due to the presence of the stabilizing agent. The drug is available under the proprietary name of Vinamar. The drug possesses a pungent odor somewhat similar to divinyl ether with a suggestion of the odor of ethyl ether. Indeed, it may be likened to a hybrid of ethyl ether and vinyl ether. The molecular weight is 72.10. The vapor is heavier than air (density 2.49 air = 1). The boiling point is close to that of ethyl ether, 35.8°C. The fact that it is less volatile than vinyl ether is said to be an advantage because *it is easier to maintain anesthesia at a desired level.* Its vapor pressure at 22°C. measured in a nitrometer is 485 mm. Hg. That of ethyl ether under the same circumstances was 471 mm. Hg.

Its solubility in water is 0.8 ml. per 100 ml. of water at 23°C. The oil/water coefficient calculated on the basis of water and oil solubility is 45 ± 5.

$$C_2H_5OH + HC \equiv CH \rightarrow C_2H_5 \!-\! O \!-\! CH \!=\! CH_2.$$

As is the case with divinyl ether, ethyl vinyl ether is unstable in the presence of acids, heat and light. It may hydrolyze to alcohol and acetylene. Ethyl alcohol (3%) is added to prevent freezing of ex-

FLAMMABILITY

As is the case with all low boiling aliphatic ethers, vinyl ethyl ether is flammable and precautions should be taken to prevent its ignition. Vinyl ethyl ether

has the same range of flammability as vinyl ether.

STABILITY

The ether is stable in the body, as far as is known, and is eliminated unchanged. It is stable in the presence of soda lime.

CYCLO-ALIPHATIC ETHERS

The successful use of ethylene and cyclopropane as anesthetics prompted the investigation of the ether related to these oxides. Krantz (1940) and his coworkers investigated a series of ethers related to the aliphatic and alicyclic hydrocarbons. Four ethers, cyclopropyl methyl, cyclopropyl ethyl, cyclopropyl propyl, and cyclopropyl butyl, have been prepared. These comprise an homologous series. The first two of three have been investigated pharmacologically and tried on man. As with other ethers, the potency increases with increase in molecular weight. The volatility and flammability decrease as the molecular weight increases. Each member of the series is prepared by interacting 1, 3, brom-2 hydroxy propane with the appropriate aliphatic ester and treating the resulting compound with zinc.

CYCLOPROPYL METHYL ETHER

Cyclopropyl methyl ether, known as *cyprome*

$$H_2C \overset{\overset{\displaystyle CH_2}{|}}{\underset{}{\diagdown}} \underset{\underset{\displaystyle H}{|}}{C}-O-CH_3$$
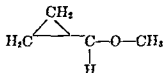
has been investigated. The ether is a colorless mobile liquid with an odor similar to cyclopropane. The specific gravity is 0.786 at 25°C. and the boiling point is 43.5° to 44°C. The vapor pressure at 26°C. is 414 mgm. Hg. The anesthetic index is 2.3. Compared with diethyl ether

it is more potent since the anesthetic index of the latter is 1.76, determined *under similar circumstances* in dogs. Seven ml., or 5.5 gms., are soluble in 100 ml. of water. The olive oil coefficient at 25°C. is 6.7 (ether 4.5). The concentration in blood is 100 mgm. per 100 ml. No evidence of oxidation in the body has been reported. Krantz believes formic acid should form in the event of oxidation in vivo, but he was unable to detect the substance in urine of animals anesthetized with the drug. Cyprome is flammable. Intimate mixtures with oxygen or air explode in as low a concentration as 2% by volume. Quantitative determinations may be conducted with the iodine pentoxide train as for other ethers.

CYCLOPROPYL ETHYL ETHER

Cyclopropyl ethyl ether,

$$CH_2 \overset{\overset{\displaystyle CH_2}{|}}{\underset{}{\diagdown\diagup}} CH-O-C_2H_5,$$
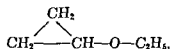
the next higher homologue to cyprome has been studied on animals and has been used in man to a limited extent. The anesthetic and chemical properties are similar in many ways to cyprome. This ether has been named *cypreth*. The boiling point, as one would expect from the increase in molecular weight, is higher than that of cyprome—68°C. The specific gravity is likewise greater —0.780 at 25°C. The anesthetic index is twice that of ethyl ether. The solubility in water is less than that of cyprome, 2.8 ml. per 100 ml., which is what one expects due to the increased molecular weight. The oil/water coefficient is higher (15.7), which is higher than diethyl ether or cyprome.

MISCELLANEOUS ETHERS

Allyl methyl ether and isopropenyl methyl ether, isomers of cyclopropyl

methyl ether, likewise have been prepared and examined for anesthetic potency by Krantz and his associates. Although both compounds exhibit narcotic potency, the former is hepatoxic, while the latter is unstable in the body and decomposes into various compounds among which is methyl alcohol. Cyprethylene ether and cypropylene ether have been prepared and are under investigation also.

ALKENE OXIDES

A group of organic oxides, referred to as *alkene oxides*, contain a cyclic structure in which an oxygen atom bridges two carbon atoms. This arrangement,

$$=C\overbrace{}^{O}C=,$$

is also known as an epoxy bridge. The simplest alkene oxide is epoxyethane, or ethylene oxide. Theoretically, this compound may be considered as ethylene which has had its double bond satisfied by the two valencies of oxygen:

$$H_2C\overbrace{}^{O}CH_2.$$

The next in the homologous series is *propylene oxide*,

$$H_2C\overbrace{}^{O}\underset{\underset{H}{|}}{C}-CH_3.$$
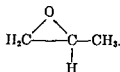
Butylene oxide follows, and so on up the series.

Ethylene oxide is a low-boiling liquid (B.P. 13°C.). The vapors are irritating when inhaled. Severe pathological changes in the lungs may result. Since the oxides have three atoms arranged in a ring, they are quite reactive. They have boiling points intermediate between the hydrocarbon and the corresponding monohydroxy alcohols of the same carbon content. Volatility decreases with increase in molecular weight. Propylene oxide boils at 35°C. None of the alkene oxides is satisfactory for anesthesia.

ACETALS

FORMATION AND STRUCTURE

Another type of organic oxide resembling ethers in structure, is a group of aliphatic compounds known as *acetals*. These are sometimes referred to as "double ethers." Some show hypnotic and anesthetic activity. Acetals are prepared by causing aldehydes to interact with alcohols. Acetaldehyde with a trace of hydrochloric or other mineral acid, and a dehydrating agent such as calcium

chloride interacts with ethyl alcohol to yield diethyl acetal or acetal proper. (See formula below.) This substance is the simplest member of the series of acetals. Others of higher molecular weight may be prepared whose structures vary with the alcohols and aldehydes used. The general reaction for their formation is typified by the equation below. The reaction may occur in steps. One molecule of alcohol interacts to form a monohy-

$$CH_3-\underset{\underset{H}{|}}{\overset{\overset{O}{||}}{C}} + 2C_2H_5OH \xrightarrow[H^+]{CaCl_2} CH_3-\underset{\underset{H}{|}}{\overset{\overset{O-C_2H_5}{|}}{C}}\overset{}{\underset{O-C_2H_5}{}} + H_2O$$
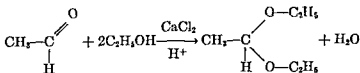
droxylated ether (CH$_3$—CHOH—OC$_2$H$_5$) known as hemiacetal. The volatility, unlike the ethers, is less than that of alcohols from which the substance is derived. Acetaldehyde boils at 21°C. and ethyl alcohol at 78°C., but the resulting acetal boils at 104°C.

ACETAL

Diethyl acetal is a colorless volatile liquid (S.G., 0.846 at 20°C.), soluble in 1 part in 18 parts of water at 20°C. The drug is very soluble in alcohol, ether, and other organic solvents. The index of refraction is 1.3819 at 20°C. Acetal is stable in the presence of alkalies. Boiling with acids converts it to the aldehyde and the alcohol. Acetals are more generally reactive than ethers. Acetal possesses hypnotic properties but is little used except as a sedative in veterinary medicine. The drug may be administered rectally, orally, or intravenously. Acetal may also be called ethylidene diethyl ether.

HALOGENATED ACETALS

Halogenated aldehydes, for example chloral, interact with alcohols to form halogenated acetals. Among these are chloralose, chloral alcoholate and so on. These are described under Halogenated Compounds (Chap. 15).

HETEROCYCLIC OXY-COMPOUNDS

Heterocyclic compounds in which one or more oxygen atom forms a ring structure with carbon are known. The heterocyclic structure with four carbon atoms and one oxygen atom is known as furan and is represented as follows:

The hydrogen atoms may be substituted by various radicals, such as aldehyde, hydroxyl, and carboxyl. Furan derivatives are not satisfactory for general anesthesia. The ring structure appears in some compounds which have local anesthetic activity, however.

Paraldehydes are heterocyclic compounds or *polyethers*, composed of three oxygen atoms alternating with three carbon atoms. These are described under aldehydes (Chap. 12).

Halogenated Compounds

GENERAL CONSIDERATIONS

HALOGENATION of certain organic compounds, particularly those of the aliphatic series, increases the number of available substances which depress the central nervous system manyfold. There are four halogens—fluorine, chlorine, bromine, and iodine. These are listed in the order of their chemical activity. Their molecules under ordinary circumstances are diatomic. Fluorine is the most active of the four. Iodine is the least useful of the four halogens as far as narcosis is concerned, since it yields compounds which are either toxic or nonanesthetic. Chlorine and bromine convert many aliphatic compounds of low narcotic potency to more potent drugs. Fluorine confers little or no narcotic effects. Indeed, in many cases fluorination decreases narcotic potency. Fluorinated compounds have not been studied in detail until recently because of difficulties in synthesis. There is at the present time considerable interest in these compounds because of availability due to improvements in methods of synthesis. Fluorinated compounds are quite different from brominated and halogenated derivatives. More will be said of them later.

Many classes of organic compounds may be halogenated. Hydrocarbons, alcohols, aldehydes, ketones, acids, esters, and ethers may all bear one or more halogen atoms on the molecule. It is customary to designate the halogen atoms in an organic compound by use of the letter "X." An aliphatic halogenated hydrocarbon would be represented by the formula RX or $C_nH_{2n}X$. Monosubstituted aliphatic hydrocarbons are termed *monohaloalkanes*, or *alkyl halides*. Those with more than one halogen are called *polyhaloalkanes*.

METHODS OF HALOGENATION

Halogenation of hydrocarbons and certain other carbon compounds is accomplished in one of two ways: (1) the halogen atom may replace a hydrogen or other atom of an aliphatic, aromatic, or cyclic compound by a reaction known as substitution; (2) the halogen may add directly to an unsaturated compound without displacement of any other atom. When chlorine and methane are mixed together, a molecule of chlorine reacts with a molecule of methane to form *methyl chloride*, or *monochlormethane*, and hydrogen chloride. The halogen replaces the hydrogen by the reaction of substitution:

$$CH_4 + Cl_2 \rightarrow CH_3Cl + HCl \uparrow$$
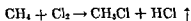
The reaction is not easily controlled and, in time, if an excess of the halogen is present, a second hydrogen atom is replaced to form dichlormethane, or *methylene chloride*, and another molecule of hydrogen chloride. A third hydrogen

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atom substitutes to form trichlormethane, or *chloroform*. Ultimately, all the hydrogen atoms are substituted if an excess of chlorine is present. The reaction for the formation of tetrachlormethane, or carbon tetrachloride, is as follows:

$$CH_4 + 4Cl_2 \rightarrow CCl_4 + 4HCl \uparrow$$
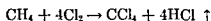
Ethane reacts in a similar manner. Ultimately, substitution of all six hydrogen atoms occurs and yields hexachlorethane. *Saturated hydrocarbons form substitution products with halogens.*

The reaction is different, on the other hand, when an unsaturated hydrocarbon, such as ethylene, reacts with chlorine. Two atoms of chlorine add directly

Hydrogen chloride does not form in this reaction because chlorine is added directly. The reaction may, of course, proceed from this point to hexachlorethane by substitution. Two halogen molecules, or four atoms of halogen are required to saturate a triple bond. Alicyclic, aromatic, and certain heterocyclic compounds either add or substitute halogens. *The type of reaction which occurs depends on the presence or absence of double bonds and the conditions of the experiment.* Benzene, for example, has three double bonds and substitutes a bromine for a hydrogen atom at 20°C. in a diffuse light in the presence of iron as a catalyst. Monobrombenzene and hydrobromic acid form:
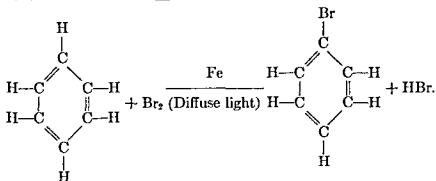
to the double bond to form 1, 2 dichlorethane, or ethylene dichloride.

$$H_2C{=}CH_2 + Cl_2 \rightarrow H_2C{-}CH_2$$
$$\qquad\qquad\qquad\quad \underset{Cl}{|} \ \underset{Cl}{|}$$
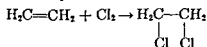
In the presence of sunlight and in the absence of the catalyst an addition product, *hexabromocyclohexane*, forms instead.
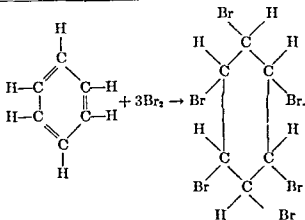
Halogenated unsaturated aliphatic hydrocarbons are also known. Vinyl chloride, dichlorethylene and trichlorethylene are important examples of these. All manifest narcotic potency.

The presence of hydroxyl, carboxyl, aldehyde, ketone, and other groups on a molecule does not prevent halogenation but does influence the position that halogen atoms assume in the molecule. Halogens may cause oxidation of certain compounds. Alcohols may be oxidized to aldehydes in the presence of a halogen. The halogens then substitute on the carbon adjacent to the aldehyde group. Ethyl alcohol is oxidized by gaseous chlorine to acetaldehyde which is then converted by substitution to trichloracetaldehyde and hydrochloric acid. (See chloral.) The halogenated aldehyde may be reduced by hydrogen aided by catalysts to trichlorethanol. A type of halogenated hydrocarbon containing one halogen and one hydroxyl group, known as *halohydrins,* may be prepared by adding hypochlorous acid (HOCl) to unsaturated compounds.

Ketones may be halogenated. The halogens attach to the alpha carbon rather than to the oxygen-bearing carbons. The same applies to acids but not to ethers. Ethers are halogenated on the carbon attached to the oxygen:

$$(C_2H_5)_2O + Cl_2 \rightarrow H-\overset{\displaystyle H}{\underset{\displaystyle H}{C}}-\overset{\displaystyle Cl}{\underset{\displaystyle H}{C}}-O-\overset{\displaystyle Cl}{\underset{\displaystyle H}{C}}-\overset{\displaystyle H}{\underset{\displaystyle H}{C}}-H.$$
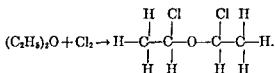
The hydroxyl, aldehyde, ketone, and carboxyl groups increase water solubility of the resulting compound when introduced into a hydrocarbon; the halogens tend to decrease it.

Although numerous completely or partially halogenated compounds are known, the aliphatic hydrocarbons, alcohols, and aldehydes containing chlorine or bromine and, to some extent fluorine, are the most important substances for anesthesia. Aromatic halogenated compounds are of no importance in anesthesia. Side chains of certain heterocyclic substances may contain one or more halogen groups, particularly if the side chain is an aliphatic derivative. Certain barbiturates are so constituted. As a rule, halogenated substances used in general anesthesia have relatively simple molecular structures and are members of the aliphatic series.

EFFECT OF HALOGENATION ON PHYSICAL PROPERTIES

Halogenation changes the chemical and physical properties of a compound. Molecular weight increases, since for each hydrogen atom a heavier atom is substituted. The fact that volatility decreases by halogenation is illustrated by the behavior of methane. Methane boils at −164°C. When converted to monochlormethane, it boils at −24°C.; to dichlormethane, it boils at 40°C.; trichlormethane, 61°C.; and tetrachlormethane, 81°C. Boiling points increase as the molecular weight increases. Fluorine, the lightest and most active of the halogens (At. Wt. 19) forms monofluoromethane, whose boiling point is −78°C. This is less than that of monochlormethane which boils at −24°C. (chlorine At. Wt. 35.46). Monobromomethane formed from bromine (At. Wt. 80) boils at 4.6°C. Methyl iodide, or moniodomethane, boils at 42.6°C. The iodine molecule is heaviest of the halogen group (At. Wt. 126). Some iodide compounds are solids. Halogenation decreases the stability of a hydrocarbon and renders the compound susceptible to

such processes as hydrolysis, oxidation, and reduction.

One important effect of halogenation from the standpoint of anesthesia is to decrease the flammability of organic compounds. Chloroform and carbon tetrachloride are non-flammable. The monohalogenated and dihalogenated derivatives of methane burn. Methane, on the other hand, will readily explode under the same conditions.

HALOGENATION AND NARCOTIC POTENCY

Narcotic potency is enhanced by halogenation. Methane has little or no narcotic effect, but as each hydrogen is replaced by a chlorine or bromine, potency increases. Methyl chloride possesses a low degree of narcotic potency and is toxic. Methylene dichloride is more potent than the former, less toxic, and more useful. Trichlormethane is more potent and the most useful of the chlormethanes. Tetrachlormethane is still more potent but considerably more toxic. Brominated compounds are more potent than chlorinated. Richardson's law applies to the halogenated hydrocarbons in the same manner as it does to the other aliphatic compounds. The potency increases as the length of the carbon chain increases. Ethyl chloride is more effective than methyl chloride, for example. The chlorethanes are less potent than the dichlorethanes. Dichlorethane is nearly as potent as chloroform.

Halogenation of alcohols also increases their potency. Trichlorethanol and tribromethanol are both more potent than ethanol. Bromination, incidentally, converts ethyl alcohol to a solid; chlorination to a liquid. Acetaldehyde is not potent and is too irritating for clinical use. Halogenation converts it to trichlor-

or tribromoacetaldehydes which are potent, useful compounds. Ethers halogenated with chlorine or bromine are not useful. Combined chlorination and fluorination has produced compounds possessing narcotic potency. Halogenated aliphatic monocarboxylic acids have little or no narcotic action and are, as a rule, irritating to tissues. Trichloracetic acid, for example, is used to cauterize tissues. Abreau and others have written concerning the effect of unsaturation on monohalogenated hydrocarbons, but have not been able to arrive at any definite conclusion regarding the effects of unsaturation upon potency. Of the halogenated olefines only the chlorethylenes are of particular interest. Hepatotoxicity appears to be less with unsaturated halogenated hydrocarbons than with saturated. In the case of hydrocarbons and ethers (ethylene, and vinethene) there is an increase in potency. Vinyl chloride,

$$H_2C=\overset{\overset{\displaystyle H}{|}}{C}-Cl,$$

possesses less toxicity but the same potency as ethyl chloride. Unsaturation decreases the volatility of the hydrocarbon. Vinyl chloride boils at −13.9°C.; ethyl chloride at 12.5°C.

Halogenated derivatives are unique in that the concentrations required for the pharmacological effects are relatively low. The effect of the halogen is to reduce volatility. This influences the relative partial pressure which develops (Chap. 27). Chloroform, for example, requires approximately 1.5% for anesthesia. This is a redeeming feature because the halogenation decreases the volatility considerably. As a rule, substances which have a boiling point of 60°C. or less are sufficiently volatile for

inhalation anesthesia. Chloroform is at the upper edge of this limit.

STABILITY IN BODY

Halogenated derivatives have been known to cause deleterious effects upon certain tissues, particularly the liver. The issues are somewhat controversial but evidence exists that some chemical change occurs which is responsible for this toxicity. A hydrolysis to hydrogen chloride or bromide and a hydrocarbon residue may be responsible for the tissue damaging properties. Although volatile halogenated hydrocarbons are exhaled unchanged through the lungs, evidence in animals of "in vivo" hydrolysis has been obtained. Abreau detected an increase in inorganic bromides in the urine after administration of bromoform to rabbits. Dresser noted increased bromides in urine after ethyl bromide inhalation by rabbits. Henderson believes this decomposition of halogens to be the basis of chronic toxicity. Compounds of $R_3 - C - X$ type liberate more inorganic bromides in vivo than

$$\begin{array}{ccc} \text{H} & & \text{X} \quad \text{H} \\ | & & | \quad | \\ R_2C{=}C{-}X & \text{or} & RC{=}C. \\ & & | \\ & & \text{H} \end{array}$$
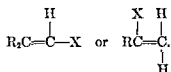
In other words, the saturated derivatives are less stable in vivo than the unsaturated.

HALOGENATED HYDROCARBONS

Hydrocarbons and ethers are the only volatile halogenated derivatives useful for inhalation anesthesia. Halogenated alcohols and aldehydes are not sufficiently volatile and are, therefore, administered by routes other than inhalation. Halogenated ketones are lacrimating and therefore not suitable. Four halogenated methanes are possible. All possess some narcotic potency, but of these four, *chloroform* possesses the greatest potency. Therefore, it is considered in detail subsequently. In the ethane group, the monohalogenated derivative, *ethyl chloride*, is a potent drug of sufficiently low toxicity for clinical use. The *dichlorethane* derivative is also anesthetic but has limited use. The higher molecular weight polyalkyl derivatives are too toxic for use. Unsaturated hydrocarbons also offer some possibility. *Vinyl chloride*, the *lowest* member of the olefin series which is halogenated, has a potency comparable to that of ethyl chloride. *Trichlorethylene* has also been used clinically. Tetrachlorethylene possesses narcotic potency but is not sufficiently volatile for satisfactory inhalation anesthesia. In the saturated series, toxicity increases as the degree of halogenation increases. Chloroform, for example, is less toxic than carbon tetrachloride. In the unsaturated series, animal experiments suggest the reverse. Trichlorethylene appears to be more toxic than tetrachlorethylene. The hydrocarbons containing bromine are not as widely employed as the chlorinated derivatives because they are not sufficiently volatile for inhalation or they possess a narrow safety margin. Aromatic halogenated hydrocarbon derivatives are non-volatile substances possessing little or no narcotic potency. A mixed halogenated ethane containing fluorine, bromine and chlorine (Halothane) is the most potent inhalational anesthetic known.

Methyl Chloride

Methyl chloride (monochlormethane),

$$\begin{array}{c} \text{H} \\ | \\ \text{H}{-}\text{C}{-}\text{Cl}, \\ | \\ \text{H} \end{array}$$

may also be considered as the methyl ester of hydrochloric acid. Methyl chloride, which is a gas, boils at —24°C. and *is easily compressed to a colorless liquid.* The compound possesses an ethereal odor and burns with a greenish flame. A hydrate forms at low temperatures ($CH_3Cl \cdot 9H_2O$). A temperature ranging from —23°C. to —55°C. is obtained by evaporating the liquid in air. The compound possesses general anesthetic properties but is rarely used clinically because it is neurotoxic. Methyl chloride is usually mixed with ethyl chloride or ethyl bromide for clinical use. These mixtures likewise are rarely used because they liberate methyl alcohol in the body and cause neuritis.

Chloroform

PROPERTIES

Chloroform, or trichlormethane, first prepared by Liebig in 1831, was introduced into surgery by Simpson at Edinburgh in 1847. This halogenated hydrocarbon is a potent anesthetic but is not widely used because of its toxic effects on cardiac and hepatic tissues. Chloroform is a colorless, mobile liquid which boils at 61°C. The drug possesses a sweet, pleasant odor. Chloroform is so potent that only a very small inhaled concentration is necessary for anesthesia (1.5%). Were it not for this fact, it would not be sufficiently volatile for inhalation. The vapor of chloroform is heavier than air

hol, ether, acetone, benzene, and all animal and vegetable fats and oils.

The index of refraction of the liquid at 20°C. using a sodium light is 1.44467; that of the vapor 1.0014364 at 760 mm. Hg. The Van der Waal's constants are (a) 15.17 and (b) 0.1022. The Raoult absorption coefficient is 1.0 g. per 100 ml. water at 15°C. The Ostwald solubility coefficient at 37°C. is 4.66 in water and 11.51 in human blood. The olive oil-water ratio at 20°C. is 70. The viscosity of the liquid at 20°C. is 0.571 centipoises, that of the vapor at 61°C. 189.0 micropoises. The melting point is —63.5°C. The latent heat of vaporization is as follows: 0°C., 64.6 gram calories, at 20°C., 62.8, at 61°C., 59.0. The heat capacity of the liquid is 0.231 gram calories at 20°C. and 0.234 at 30°C.

PREPARATION

Chloroform may be prepared in a number of ways. The classical method, and one which may be used in the laboratory, is to heat acetone or ethyl alcohol with bleaching powder ($CaOCl_2$) and to subject the mixture to steam distillation. Alcohol is first oxidized to acetaldehyde by the chlorine which is liberated from the bleaching powder. The methyl group is then halogenated by substitution to form trichloracetaldehyde. If acetone is used, one of its methyl groups is chlorinated by substitution to form trichloracetone:

$$CH_3-\overset{\overset{\displaystyle O}{\|}}{C}-CH_3 + 3Cl_2 \rightarrow Cl-\overset{\overset{\displaystyle Cl}{|}}{\underset{\underset{\displaystyle Cl}{|}}{C}}-\overset{\overset{\displaystyle O}{\|}}{C}-CH_3 + 3HCl.$$
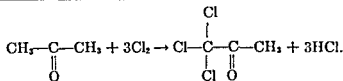
(S. G. 4.12, air = 1). Unlike ether, the liquid sinks in water since it has a specific gravity of 1.476 at 20°C. Water solubility is low—0.822 ml. per 100 ml. at 20°C. The drug is miscible with alco-

Both trichloracetone and trichloracetaldehyde react with alkalies to form chloroform and salts of organic acids. Bleaching powder supplies the alkali as it yields calcium hydroxide in this reaction. Cal-

cium acetate forms, illustrated by the following reaction:

$$2Cl-\overset{\overset{\displaystyle Cl}{|}}{\underset{\underset{\displaystyle Cl}{|}}{C}}-\overset{\overset{\displaystyle O}{\|}}{C}-CH_3 + Ca(OH)_2 \rightarrow 2Cl-\overset{\overset{\displaystyle Cl}{|}}{\underset{\underset{\displaystyle Cl}{|}}{C}}-H + Ca\overset{\overset{\displaystyle O}{\overset{\displaystyle \|}{O-C-CH_3}}}{\underset{\underset{\displaystyle O}{\|}}{O-C-CH_3}}$$
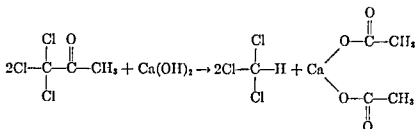
Chloral hydrate is also converted to chloroform by alkalies, Bromal, tribromacetaldehyde, and triiodoacetaldehyde are likewise decomposed to their respective haloforms and salts of organic acids. Chlorine or bromine water boiled with acetone or ethyl alcohol will form chloroform or bromoform. The reaction is essentially similar to that obtained with bleaching powder.

Commercially, chloroform may be prepared in large quantities by allowing carbon tetrachloride and hydrogen to react in the presence of iron by the following reaction:

$$Cl-\overset{\overset{\displaystyle Cl}{|}}{\underset{\underset{\displaystyle Cl}{|}}{C}}-Cl + 2H \overset{Fe}{\longrightarrow} Cl-\overset{\overset{\displaystyle Cl}{|}}{\underset{\underset{\displaystyle Cl}{|}}{C}}-H + HCl.$$
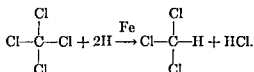
STABILITY

Chloroform for anesthesia has added it to 1% ethyl alcohol for purposes of stabilization. The drug is best stored in dark bottles away from heat, light, and contact with air, all of which favor oxidization to phosgene (carbonyl chloride),

$$\overset{Cl}{\underset{Cl}{\diagup\!\!\diagdown}}C{=}O.$$

Phosgene has been used as a poison gas in warfare. It reacts with water to form hydrochloric acid and carbonic acid. If the gas is inhaled, this reaction occurs in the respiratory tract. The gas itself is not pungent and is easily inhaled. The hydrochloric acid has an irritating action upon mucous membranes and produces pulmonary edema. Alcohol is added to chloroform as a preservative. The phosgene which forms in anesthetic chloroform reacts with the added alcohol to yield diethyl carbonate, a comparatively harmless ester. The acid yields ethyl chloride with alcohol:

(See formula at bottom of this page)

The physiological behavior of chloroform lends support to the Meyer-Overton theory of narcosis (Chap. 27). The low water solubility, coupled with high lipoid solubility, results in a high partition coefficient. At 20°C. the coefficient is 100. Chloroform is stable in the body and is eliminated unchanged.

FLAMMABILITY

Chloroform is not ignited by sparks, or flames, and, therefore, does not form

$$2C_2H_5OH + \overset{Cl}{\underset{Cl}{\diagup\!\!\diagdown}}C{=}O \rightarrow \overset{C_2H_5O}{\underset{C_2H_5O}{\diagup\!\!\diagdown}}C{=}O + 2HCl.$$
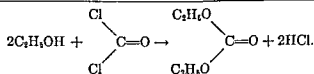
explosive mixtures. Oxidation of chloroform vapors if exposed to flames yields phosgene. Phosgene may form if chloroform vapor is exposed to cautery, sparks, or other heating devices used during operation.

$$\text{C}_6\text{H}_5-\text{NH}_2 + \text{CHCl}_3 + 3\text{NaOH} \rightarrow \text{C}_6\text{H}_5-\text{N}\equiv\text{C} + 3\text{NaCl} + 3\text{H}_2\text{O}.$$

DISTRIBUTION IN TISSUES

The concentration in blood necessary for surgical anesthesia ranges between 40 and 50 mgm. per 100 ml. Blood concentrations reported by different authors are in wide ranges of disagreement, probably due to the methods of analysis and variation in depth of anesthesia. Lethal concentrations appear to be above 80 mgm. per 100 ml. Approximately twice as much is transported by the red cells as by plasma. The concentration in brain tissues is 30–45 mgm. per 100 gm. of tissues during moderate anesthesia in dogs. Although it is almost all entirely exhaled unchanged from the lungs its stability in the body has been questioned from time to time. The administration of compounds containing bromine produces anesthesia which is followed by an increased excretion of inorganic bromides in urine. Chloroform may possibly behave similarly and form hydrochloric acid and a residual hydrocarbon. This is difficult to prove because the resulting chlorides are difficult to differentiate from the normally occurring chlorides. The urinary excretion of chloroform is in proportion to and usually parallels the concentration in plasma. Lipoid tissues, as one would expect, absorb more of the drug than other tissues.

IDENTIFICATION

Chloroform is chemically reactive. It interacts with aniline in the presence of sodium hydroxide to form phenyl isocyanide, a substance with a disagreeable odor:

The reaction is called the Hoffman carbylamine reaction. Alpha and beta naphthol in 33% sodium hydroxide react with chloroform to form a compound with a brick red color. Chloroform is analyzed by means of Fugiwara color reaction. Halides of the type RCX_3 react with pyridine in sodium hydroxide to form a derivative with a pink color. The test, which has a sensitivity of 1 part per million for chloroform, forms the basis of the Cole test. The Cole test is used to identify and quantitatively determine chloroform in body fluids and tissues. The resultant color is compared colorimetrically, using a standard composed of aqueous solutions of cobaltous salts. In toxicological studies the chloroform is isolated by steam distillation and the test is applied to the distillate. Toxicological material, body fluids, and other biologicals, must be examined immediately because chloroform quickly decomposes to formic acid. Chloroform is easily hydrolyzed by alkalies to formates. The gas chromatograph appears to be a useful tool for analytical studies of halogenated hydrocarbons. More accurate data concerning blood and tissue concentrations will be evolved as techniques of analysis are developed. Chloroform tagged with radioactive chlorine has been used for studying the distribution in the body. Soda lime for carbon dioxide

absorption in rebreathing appliances may convert some of the chloroform to calcium formate and sodium formate. Also some dichloracetaldehyde may form which is irritating.

$$CHCl_3 + 4NaOH \rightarrow HCOONa + 3NaCl + 2H_2O.$$

IMPURITIES

Chloroform for anesthesia should be free of all impurities of manufacture, decomposition, and contamination. Phosgene is the most important and dangerous impurity in chloroform. Acetone, free halogens, organic halides, hydrochloric acid, organic acids, ethyl chloride, ethyl carbonate, aldehydes, and peroxides are other possible impurities.

Qualitative tests are available to detect these impurities. If a portion of pure chloroform is washed with an equal volume of water, the aqueous layer should be neutral to litmus. The aqueous layer should also be free from halogen ions which may be detected by means of acidified silver nitrate solution. Free chlorine or other halogens may be detected by adding several drops of neutral 10% potassium iodide solution to a portion of the aqueous layer. Chlorine, which is more active than iodine, displaces free iodine which is identified by the blue color it yields with starch. Ketones and aldehydes may be detected by adding several drops of Nessler's solution to a portion of the aqueous layer. A precipitate forms if the test is positive.

Pure specimens of chloroform should be free from residue and odor upon evaporation to dryness over a water bath. Carbonizable substances should be absent when a portion of chloroform is treated with concentrated sulphuric acid.

Chloroform is included in the U.S.P.

Carbon Tetrachloride

PREPARATION

Carbon tetrachloride was first prepared by Regnault in 1839 by interacting chlorine and chloroform. The commercial product is prepared by passing carbon disulphide and chlorine over a catalyst containing antimony pentachloride.
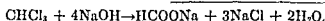
PROPERTIES

Carbon tetrachloride is a clear, colorless, nonflammable, heavy liquid with a chloroform-like odor. It boils at 76.7°C. and has a specific gravity of 1.589 at 25°C. The solubility in water is low—1 part in 2000 parts of water. It is miscible with alcohol, chloroform, ether, and other organic solvents. Carbon tetrachloride possesses anesthetic properties but its toxicity on the liver is pronounced. The margin of safety if used for inhalation is narrow. The drug is cardiotoxic also.

Ethyl Chloride

PREPARATION

The general anesthetic properties of ethyl chloride were first described in animals by Flourens in 1847 and Heyfelder in 1848. This observation was overlooked until Carlson, in 1894, reintroduced it as a general anesthetic in dentistry.

Ethyl chloride, or monochlorethane, may be considered either as an ester of ethyl alcohol and hydrochloric acid or the monohalogen substituent of ethane. The drug may be prepared by treating ethyl alcohol with hydrochloric acid in the presence of zinc chloride:

$$C_2H_5OH + HCl \rightarrow C_2H_5Cl + H_2O.$$
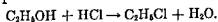
An alternate method of preparation is to add hydrogen chloride to ethylene. A completely saturated compound forms.

$$H-\underset{\underset{H}{|}}{\overset{\overset{H}{|}}{C}}=\underset{\underset{H}{|}}{\overset{\overset{H}{|}}{C}}-H + HCl \rightarrow H-\underset{\underset{H}{|}}{\overset{\overset{H}{|}}{C}}-\underset{\underset{H}{|}}{\overset{\overset{H}{|}}{C}}-Cl.$$
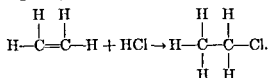
PROPERTIES

Ethyl chloride is sometimes referred to as "kelene." The substance is a gas at ordinary temperature and pressures but is easily compressed into a colorless, highly volatile liquid, which can be stored in glass or metal tubes equipped with a spring cap covering a pinhole exit. The liquid boils at 12° to 13°C. and solidifies at —140°C. When sprayed on the skin in a fine stream, a temperature of —20°C. is attained which causes the tissues to freeze. Water vapor from the patient's exhalation freezes on the mask during inhalation forming a frost. The frost which forms is not solid ethyl chloride, as is erroneously believed by some clinicians. The latent heat of vaporization is 92 calories per gram at 25°C. The liquid floats upon water (S.G. 0.921 at 20°C.), in which it is very slightly soluble.

FLAMMABILITY

Ethyl chloride is not too far removed from ethane since it is only monochlorinated. Therefore, it possesses flammable properties and explodes when mixed with air in as low a concentration as 4% to 14.5% at 25°C. and atmospheric pressure. In oxygen the range of flammability is 4.05 — 67.2. The ignition temperatures of flammable mixtures is 517°C. in air and 486°C. in oxygen at atmospheric pressure and room temperature (25°C.). The vapor is 2.28 times heavier than air.

IMPURITIES

Ethyl chloride may contain traces of alcohol. Aldehydes, chlorides, or polyhalogenated ethanes may be some other impurities.

DISTRIBUTION IN TISSUES

The anesthetic concentration in volumes per cent ranges from 3% to 4.5%. The blood concentration during surgical anesthesia ranges between 20 mgm. and 30 mgm. per 100 ml. of blood. Ethyl chloride is lipophilic. The Raoult absorption coefficient is 0.574 gm./100 ml. water at 20°C. The Ostwald solubility coefficient at 20°C. is 2.1 for water and 65 for olive oil. At 37°C. it is 40.5 for olive oil. The drug is eliminated unchanged by exhalation. Whether or not it undergoes any deterioration in the body is not known.

Trichlorethane

PROPERTIES

The anesthetic effects of trichlorethane have been studied by Krantz and his coworkers. The substance is a dicarbon molecule having three chlorine atoms on a single carbon. It is a nonflammable liquid which boils at 74.1°C. The odor resembles chloroform. The liquid tends to deteriorate into various halogenated products unless preserved with 0.01% thymol. The anesthetic properties and potency are similar to chloroform. The period of induction is short (3 to 4 minutes) while recovery requires twenty to thirty minutes. Its behavior is similar to that of chloroform in this respect.

SOLUBILITY

The solubility in water is 0.19 ml. in 100 ml. at 30°C. The oil/water coefficient is 100.

Isopropyl Chloride

Isopropyl chloride is a saturated halogenated hydrocarbon. It is a colorless liquid with a garlic like odor. It is flammable and forms explosive mixtures when the vapor is mixed in air and oxygen. It decomposes when exposed to sunlight or heat to hydrochloric acid and various halides. It has a boiling point of 36.5°C., a molecular weight of 78.5, a specific gravity of 0.8558 at 20°C. It is sparingly soluble in water, 0.308 grams in 100 ml. at 20°C. but is miscible with alcohol and ether.

In animal experiments its anesthetic potency is approximately double that of diethyl ether. Concentrations of ½ to 1.2 volumes per cent in the inspired atmosphere produce anesthesia in dogs. It was introduced as a clinical anesthetic agent by McDonald in 1950. Unfavorable results from clinical use have been reported by Lockett, Elam, Dodd and others. Generally, it is regarded in the same category as ethyl chloride and behaves similarly in regards to the cardiac tissues. It produces a rapid induction and emergence and is non-irritating to the pharynx, larynx, trachea and bronchi.

Vinyl Chloride

Vinyl chloride was investigated for anesthetic potency by Krantz and his coworkers (1947). The substance is used in industry for the synthesis of various organic compounds. Vinyl chloride is a gas which boils at −15°C. It is soluble in the usual organic solvents. The vapors are combustible. The action of vinyl chloride is similar to that of ethyl chloride and less harmful than either chloroform or carbon tetrachloride. The concentration for anesthesia for man is 7—10%. In general it has little to offer over ethyl chloride and its use is considered unsafe.

Dichlorethylene

Dichlorethylene is another of the halogenated olefines. It is also known as acetylene dichloride and as Dioform. It is a liquid with an ethereal acrid odor which boils at 55°C. The vapors produce anesthesia, but the drug has never had clinical application. The drug is decomposed by heat and light to hydrochloric acid and various halides.

Trichlorethylene

DESCRIPTION

Trichlorethylene,

$$H-\overset{\overset{\displaystyle Cl}{|}}{C}=\overset{\overset{\displaystyle Cl}{|}}{C}-Cl,$$

is an unsaturated, halogenated hydrocarbon. It has been known under various names, such as chlorylene, Westrosol, Ethenyl trichloride, Trimar and Trilene. Trichlorethylene was first described in 1864 by the German chemist Fischer. The substance has been widely used as a solvent for fats and oils, particularly in the dry cleaning industry. Plessner in 1915 accidentally discovered its analgesic properties and described its toxic manifestations. The drug was believed to possess a selective action on the trigeminal nerve and was introduced into medicine principally for relief of trigeminal neuralgia. The general anesthetic properties were overlooked for some time. The anesthetic effects were first discovered in animals by Lehmann in 1911. Dennis Jackson and his co-workers (1934) became interested in central analgesic actions of trichlorethylene and administered the drug to dogs. He believed that trichlorethylene was a useful drug but was discouraged by a report from the Council on Pharmacy and Chemistry which suggested that additional work was necessary. The search for nonflam-

mable anesthetics led to a revival in interest. Hewer in 1940 gave a preliminary report on 127 cases.

PREPARATION AND PROPERTIES

Trichlorethylene is prepared by boiling symmetrical tetrachlorethane with lime. The drug is a clear, colorless, nonflammable liquid possessing an odor somewhat like that of chloroform. As is the case with most halogenated hydrocarbons it is heavier than water. The specific gravity of the liquid is 1.45 at 25°C. The refractive index is 1.4770 at 25°C. The boiling point is somewhat higher than that of chloroform (88 to 90°C.). This is a disadvantage since adequate vapor pressures to maintain anesthesia are obtained with difficulty. Like chloroform it is insoluble in water but miscible with alcohol, ether, oil and other organic solvents. The density of the liquid is 1.4980 grams per ml.; that of the vapor at its boiling point is 0.00445. The viscosity at 20°C. is 0.58 centipoises; that of the vapor 0.103 micropoises at 60°C. The molecular weight is 131.3. The melting point is −73°C. The latent heat of vaporization is 57.24 gram calories. The heat capacity of the vapor is 0.156 gram calories at 80°C. and 1 atmosphere; that of the liquid is 0.233 gram calories at 20°C. The Van der Waals' constants are $a = 16.980$ and $b = 11.280$. The absorption coefficient is 0.11 gram per 100 grams of water at 25°C. The Ostwald solubility coefficient at 20°C. is 3.0 for water, 18–22 for human blood and 15–20 for plasma. At 37°C. the coefficient is 1.55 for water and 8–10 for human blood. The commercial preparation may contain impurities, therefore, only the purified agent should be used for anesthesia. In England trichlorethylene is produced under the name of Trilene. Thymol

(.01%) is added to retard decomposition. In addition waxoline blue, 1–200,000, is added to avoid confusing the drug with chloroform. The pure drug decomposes in strong light and air and should be stored in tinted bottles or stoppered cans. The drug should never be used after exposure to air and standing for more than one or two days in its usual container. Acid products such as phosgene, acetylene, acetylene dichloride and hydrochloric acid form. The substance contributes to an industrial hazard. Poisoning has been reported in establishments where it is employed as a solvent.

FLAMMABILITY

Trichlorethylene is not flammable in ordinary anesthetic concentrations. Concentrations of 10.3–64.5% in oxygen or oxygen-rich mixtures at temperatures exceeding 25.5°C. will ignite. The vapor pressure is too low below this temperature to form a flammable mixture. The minimum ignition temperature is 419°C. in air and 463°C. in oxygen. Trichlorethylene used in the presence of a cautery causes the formation of varying amounts of phosgene but this is believed by many to be of doubtful importance in clinical practice. Mixtures in air are not flammable.

DISTRIBUTION IN TISSUES

The inhaled concentration for analgesia varies from 0.25%–0.50%. Inhaled concentrations for surgical anesthesia average 4%. In blood the concentration in dogs varies between 20–30 mg. per cent. The concentrations producing respiratory failure in dogs are 110–100 mg. In humans the concentration appears to be lower averaging 6.5–12.5 during clinical anesthesia. The blood concentration falls to 1 mg. within three hours on

cessation of anesthesia and to 0.10% in 24 hours.

Unlike the majority of inhalational anesthetics, trichlorethylene undergoes some change in the body. Trichloracetic acid appears in the urine during the first 24 hours in concentrations that vary with the amount of trichlorethylene administered and the duration of anesthesia. Trichloracetic acid blood levels are increased for two or three days after the administration of the drug. The trichloracetic acid level gradually declines within five days. It is believed that the compound is first converted to trichlorethanol and is then oxidized to trichloracetic acid. The initial product of metabolism in dogs is trichloracetic acid. These metabolites continue to appear in the urine for as long as 6–10 days. The unconverted portion is eliminated from the urine through the lungs. Traces are found in the expired air for as long as 48 hours.

STABILITY WITH SODA LIME

Trichlorethylene is unstable in the presence of alkalies. It forms dichloracetylene in the presence of soda lime in the closed circuit. Dichloracetylene *causes a toxic neuritis. The fifth and seventh cranial nerves seem to be most frequently involved. However, the third, fourth, sixth, tenth and twelfth also have been affected. The dichloracetylene is spontaneously flammable and forms phosgene and carbon monoxide upon standing. The decomposition occurs gradually and is retarded by the presence of excess trichlorethylene or ether. Dichloracetylene, therefore, may linger when in the apparatus and in the soda lime granules. Patients in subsequent anesthetization may be affected by the toxic products for as long as 3 or 4 days after the absorbent is contaminated. The

patient exhaling the trichlorethylene into the soda lime may cause dichloracetylene to form but not receive enough of the toxic product to cause nerve palsies. Data from animals suggest that the hazard of dichloracetylene formation is diminished if an interval of 15 minutes or more elapses from the time the trichlorethylene is discontinued and closed system anesthesia is commenced. The quantity of trichloracetylene which forms increases as the temperature from the soda lime in the canister rises. The relationship, however, is not necessarily a linear one. The rate of the formation rises abruptly above 60°C. Inasmuch as one never has the assurance that toxic byproducts will not form it is advisable not to use closed system anesthesia after trichlorethylene has been employed.

The presence of free acids in specimens of trichlorethylene may be detected by the use of Congo red or other indicators. Free chlorides may be determined by the use of dilute silver nitrate solution in nitric acid. Trichlorethylene has been analyzed qualitatively and quantitatively by the Fugiwara Reaction, the iodine pentoxide train, and *the interferometer.*

Tetrachlorethylene

DESCRIPTION

Tetrachlorethylene,

$$\begin{array}{c} \text{Cl} \quad \text{Cl} \\ | \qquad | \\ \text{C}{=}\text{C} , \\ | \qquad | \\ \text{Cl} \quad \text{Cl} \end{array}$$

also known as perchlorethylene, is an unsaturated halogenated hydrocarbon employed chiefly as an anthelmintic. The drug was first prepared by Faraday. Its narcotic properties were first noted in 1911 and then investigated by Lehmann

and his associates in 1936. Lamson, Robinson, and Ward studied the pharmacologic properties.

PROPERTIES

The drug is a heavy, colorless liquid with a sweet but not unpleasant odor. The specific gravity of the liquid is 1.6311 and its boiling point is 121°C. The vapor, which is extremely heavy (S.G. 5.72), is not flammable when mixed with air or oxygen at ordinary temperatures (25°C.). The drug is soluble in organic solvents, such as alcohol, chloroform, and benzene, and is miscible in all proportions with vegetable and mineral oils. It is poorly soluble in water (1/2500 at 30°C.).

ANESTHETIC POTENCY

Apgar and her associates, in search of a potent nonflammable anesthetic, attempted to use the drug for anesthesia in man (1942). Considerable difficulty was experienced in vaporizing the liquid to obtain the concentration necessary for surgical anesthesia. Induction was prolonged and maintenance of an even plane of anesthesia was impossible. Although they found the drug to be a potent anesthetic, it was objectionable because of irritation to tissues of the respiratory tract, burns to the skin, and copious secretions.

Tetrachlorethylene is stable when stored in amber bottles away from air and light. Light and heat cause its decomposition. Phosgene and hydrochloric acid are among its products of decomposition.

Ethyl Bromide

Ethyl bromide, or monobromoethane, is prepared by distilling a mixture of potassium bromide, alcohol, and sul-

phuric acid. Like ethyl chloride, ethyl bromide is a volatile liquid with an ethereal odor and a burning taste. However, it is less volatile than ethyl chloride (B.P. 38° to 40°C.). The specific gravity of the liquid is 1.429 at 25°C. One part is soluble in 100 parts of water at 0°C. Water solubility decreases as the temperature increases. In the presence of air and light, ethyl bromide decomposes. Free bromine frequently forms. Ethyl bromide as such is little used in anesthesia. A mixture of ethyl chloride, methyl chloride, and ethyl bromide has been also used for inhalation anesthesia in man but is now obsolete.

Bromoform

PREPARATION

Bromoform, or tribromoethane, was first prepared by Löwig in 1832. The substance is prepared by halogenation of acetone, by warming with bromine water and sodium hydroxide. The reactions are similar to those used for the preparation of chloroform.

Bromoform is a colorless, heavy liquid, which boils at 249° to 250°C., and possesses an odor somewhat similar to chloroform. Bromoform has a specific gravity of 2.902 at 25°C. Like chloroform, its solubility in water is low, approximately 1/800 at 25°C. The drug is miscible with the organic solvents and in fats. Bromoform decomposes readily if exposed to light and heat. Approximately 3% to 4% alcohol is added as a preservative. Products of decomposition are various brommated substances and free bromine. Bromoform is unimportant clinically.

FLUORINATED COMPOUNDS

Fluorine and fluorinated compounds have been known for some time. Henri

Moissan isolated fluorine in 1886. The intense interest in fluorinated hydrocarbons as solvents, refrigerants, etc. which has developed in recent years obscures the fundamental fact that the chemistry of these compounds has been known for some time. Quantities available for study were limited. Methods of synthesis, although difficult, have improved considerably. Organic fluorinated compounds manifest properties which can be characterized as extremes or as opposites. Some are highly reactive; others are extremely inert. Some are toxic; others are non-toxic. Compounds containing a single fluorine atom attached to a carbon differ markedly from those containing two or three fluorine atoms. Alkyl derivatives, with a single fluorine atom, are unstable and hydrolize easily to an alcohol and hydrofluoric acid. The difluorides (sometimes called gem fluorides) are more stable but do undergo chemical change. The trifluoro

$$F-\overset{\overset{\displaystyle F}{|}}{\underset{\underset{\displaystyle F}{|}}{C}}-R$$

compounds are extremely stable. Fluorine may replace hydrogen in a series of hydrocarbons to form a comparable fluorinated series.

Hydrocarbons whose hydrogen atoms are substituted by fluorine are referred to as *fluorocarbons*. Fluorocarbons are extremely inert, being almost as stable as the inert gases. They react only when subjected to vigorous chemical activity. They react with metallic sodium and potassium heated to 300°–400°C. They react with silica at about 400°C. to form silicon tetrafluoride. The purely fluorinated hydrocarbons are without narcotic potency. CF_4 is an extremely stable, inert

compound while CCl_4 is quite potent. The presence of two fluorine atoms reduces the narcotic activity and toxicity of chlorine atoms attached to the same carbon atom. The reactivity of CF_2Cl_2 both chemically and physiologically is less than that of CH_2Cl_2. The progressive replacement of hydrogen by chlorine, bromine or iodine causes a continued increase in boiling point. The situation is different with fluorine. A progressive replacement of hydrogen by fluorine in a carbon atom causes an initial increase in boiling point followed by a decrease. For example: CH_4 boils at −161°, CH_2F_2 at −52°, CHF_3 at −83°, CF_4 at −128°C. The same holds for mixing halogens. For example: CH_2Cl_2 boils at −24°, CH_2ClF boils at −9°, $CHClF_2$ boils at −41°, while $CClF_3$ boils at −81°C. Fluorination reduces the flammability of the compound. Fluorination of the aromatic ring causes little change in boiling point. Fluorine is the most electronegative of elements. It, therefore, exerts a pronounced effect on other halogens which appear with it on a carbon atom and confers greater stability to the molecule. The interatomic distance is shortened progressively as the number of fluorines increases on an atom. The attraction between molecules decreases, thereby decreasing the boiling point. This marked electronegativity appears to be transmitted to adjacent carbon atoms. In the case of halothane the bromine and chlorine atoms on the adjacent carbon atom are attached more tenaciously than they are in the corresponding hydrocarbon. The presence of the CF_3 group confers marked stability to a molecule particularly if it is one composed of several carbon atoms.

A series of fluorocarbons often referred to as *freons* have been produced

which, by virtue of their low boiling points, nonflammability, and inertness, are used as refrigerants. Dichlorodifluoro methane (Freon-12) is used as a solvent-propellent for aerosols and as a refrigerant. It is non-narcotic.

The interest in the anesthetic potency of fluorinated derivatives goes back a number of years. Robbins (1946) investigated the anesthetic properties of a series of 46 saturated, unsaturated, fluorinated and mixed halogenated aliphatic hydrocarbons and ethers of four carbon atoms or less. He found four of these to be of interest. These were (CF₂CHCl CHCl), (CHF₂CHCl · CHCl · CH₂Cl), (CF₂CHBr₂) and (CF₂CHBr₂CH₃). They all produced arrhythmias, falls in blood pressure and poor muscle relaxation. The amounts available to him were limited—less than several ml. Their purity was not established with certainty. Krantz and his co-workers (1953) likewise studied an extensive series in which he found trifluoroethyl vinyl ether (Fluoromar) to be the most promising. Suckling, Raventos, Johnstone and others in Great Britain found alpha trifluoro beta monochlormonobromethane to be extremely potent and introduced it under the name of halothane (Fluothane). Artusio investigating a series of refrigerants found difluro, dichloroethyl methyl ether (Methoxyfluorane) to offer some promise.

In general the substitution of fluorine for chlorine decreases the potency, toxicity and anesthetic activity of hydrocarbons and ethers. Those of promise thus far are *mixed compounds which have other halogens or ether linkages in the molecule.* Complete fluorination of methane produces an inert compound which Faulconer found to be non-anesthetic. Complete substitution of all hydrogen atoms on ethyl ether produce a

convulsant. One hydrogen atom at least appears to be necessary for anesthetic activity on each alkyl radical.

Halothane (Fluothane)

PROPERTIES

In searching for a potent nonflammable anesthetic, Suckling and his co-workers in 1956 synthesized 1,1,1,1,trifluoro 2,bromo, 2,chloroethane:

$$F-\overset{\overset{\displaystyle F}{|}}{\underset{\underset{\displaystyle F}{|}}{C}}-\overset{\overset{\displaystyle Cl}{|}}{\underset{\underset{\displaystyle H}{|}}{C}}-Br.$$
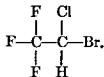
This compound known as halothane (Fluothane) is a colorless, clear, somewhat heavy volatile liquid with a sweet pleasant odor somewhat resembling chloroform. The molecular weight is 197.39, its boiling point is 50.3°C. The specific gravity (density) is 1.86 at 15°C. The solubility in water is 0.0345 gm. per ml. at 20°C.; 0.0160 gm. per ml. of blood at 37°C.; oil-water ratio is 330 at 23°C. The partition coefficients for air-water are 0.87 at 23°; for air-blood 0.16 at 23° and 0.28 at 37°C. The refractive index is 1.3695 to 1.3705 for the D line at 20°C. At the boiling point the latent heat of vaporization is 35.2 calories per gram. The viscosity is 0.319 centipoises for the liquid at 30°C. The specific heat is 0.003 calories per gram at 25°C. The vapor pressure at 10°C. is 157 mm. Hg, at 20°C. 243 mm. Hg, at 30°C. 364 mm. Hg. Vapor pressure for other temperatures may be calculated:

$$\log p = 7.723 \times \frac{1565}{T}$$

in which $T =$ absolute temperature and $p =$ vapor pressure in mm Hg.

STABILITY

Halothane is not flammable in any proportions with air or oxygen. It is

stable in the presence of soda lime. It is slowly decomposed by light to hydrochloric acid, phosgene and other mixed halogens. This deterioration is inhibited by the addition of 0.01% Thymol. Halothane reacts with certain metals in the presence of moisture due to the liberation of acids. It attacks aluminum and zinc but not copper. It may cause expansion of some plastics and deterioration of rubber after long exposure. The presence of three fluorine atoms imparts unusual properties to the molecule. The compound has an asymmetric carbon atom and should, therefore, have two optical isomers. However, it has not been resolved into its isomers.

POTENCY

Fluothane is the most potent inhalational anesthetic known. Full surgical anesthesia is obtained with a concentration of 2–4% within 2–5 minutes. Maintenance requires 0.4–1%. Blood concentrations vary from 4–9 mgm. percent during light anesthesia; 22 mgm. percent during surgical anesthesia and 28–35 mgm. percent at a depth sufficient to cause respiratory arrest. Ten minutes after anesthesia the blood concentration falls to 0.8 mgm. percent or less. The drug is stable in the body. Elimination is almost entirely by exhalation.

AZEOTROPIC MIXTURES

An azeotropic mixture is a mixture of two or more volatile substances mixed in such proportions that the combined vapor pressure of each equals atmospheric pressure. In other words, they will distill without decomposition in a certain ratio at a constant boiling temperature. The mixing of two or more volatile agents is designed to take advantage of the beneficial properties of each agent and, at the same time, minimize the disagreeable properties of each. This has been common practice for many years. John Snow used mixtures of chloroform and ether. Their use has been common with the halogenated compounds in particular. Thus, it is not surprising to find that ether has been combined with halothane. An azeotropic mixture forms when 31.7% ether and 68.3% halothane are mixed. The azeotropic mixture of halothane is designated to minimize side effects of the halothane and decrease the quantity used. The mixture distills at 51.5°C. The two drugs are compatible; therefore, a stable mixture forms. The mixture of the vapor mixed with air or oxygen is not flammable if the concentration remains less than 10.7% by volume. Above this the mixture is flammable. The partial pressure of the mixture at 24°C. is 742 mm. Hg. The partial pressure necessary for anesthesia is 11.1 mm. Hg (1.5% by volume).

Trifluoroethyl Vinyl Ether

PROPERTIES

Trifluoroethyl vinyl ether is a halogenated, unsaturated ether having three fluorine atoms on the terminal carbon of the ethyl group. It does not have a chlorine or bromine in the molecule. The compound was first prepared in 1951 by Shukyse. The anesthetic properties of the ether were studied by Krantz and his co-workers (1952) in animals and by Orth, Dornette, Dripps and others in man. The drug is made by the interaction of acetylene and trifluoroethanol.

PROPERTIES

Trifluoroethyl vinyl ether is a mobile, colorless liquid with an odor similar to vinyl ether. The vapor is non-irritating. Its boiling point is 43.2°; specific gravity

is 113 at 25°C. The vapor is heavier than air, 4.4 air = 1. The vapor pressure is 28°C. at 395 mm. Hg. The molecular weight is 126. The index of refraction is 1.3192 at 20°C. using a sodium light.

STABILITY

The molecule is fairly stable; it can only be disrupted by drastic treatment with alkalies. It does not hydrolyze in buffered solutions whose pH ranges from 2 to 11. It has none of the chemical properties of inorganic fluorides. It does not release fluoride when it is in contact with soda lime. It is stabilized with 0.01% phenyl naphthylamine, as is vinyl ether. Light causes the ether to decompose to acetaldehyde and trifluoroethanol. For this reason it is stored in brown bottles with a stabilizer (phenyl α naphthylamine 0.01%).

SOLUBILITY

It is soluble 0.4 vols. percent in water at 30°C. The oil-water ratio in corn oil at 25°C. is 90. The air-blood ratio is 5:1. Induction is rapid, recovery is rapid. The inhaled concentrations in man are as follows: For analgesia—1.2%-2%; plane one —1.2%-3.2%; plane two—2%-3.3%; plane three—3%-5%; plane four—5%-8%. The vapor is stable in the presence of soda lime.

ELIMINATION

The ether is eliminated unchanged through the lungs. Blood levels for light anesthesia are 10–20 mgm. per 100 ml., 12–30 for moderate and 18–35 for deep. Blood levels after 35 minutes dropped from 42 mgm. percent, after one hour to 10.0 mgm. percent, after three hours to 3.9 mgm. percent, after six hours to 3.0 mgm. percent. The lethal blood level is 40–60 mgm. percent.

FLAMMABILITY

In spite of halogenation the drug is flammable. The fluorine atoms, however, do reduce the flammability somewhat but do not completely suppress it. The lower range of flammability is 4.1% in air and 4.0% in oxygen. Energy required to ignite a flammable mixture is 30 times that required to ignite ethyl ether.

Sulphur Hexafluoride

Sulphur combines with fluorine to form an extremely stable gaseous compound which has an anesthetic potency similar to nitrous oxide but somewhat more feeble. The compound is so stable and inert that it withstands boiling in sodium hydroxide, temperatures equal to those necessary to soften glass and electric potentials up to 5½ million volts. Its narcotic activity is physical rather than chemical due to the inertness. The inertness is associated with the strong electric negativity of the fluorine atom which causes a strong covalent bonding. The solubility coefficient is 0.1 at standard conditions. This is less than that of helium, which is the least stable of the elemental gases and which has a coefficient of 0.87. The oil solubility is high compared to helium —2 for helium and 21 volumes percent for sulphur hexafluoride. The oil water ratio is 200 at 20°C. Virtue found the inhaled concentration in man to 79%.

Methoxyflurane

Methoxyflurane is a chlorinated fluorinated ether studied experimentally by Artusio and Van Poznak. The structure is as follows:

$$H-\overset{\overset{\displaystyle Cl}{|}}{\underset{\underset{\displaystyle Cl}{|}}{C}}-\overset{\overset{\displaystyle F}{|}}{\underset{\underset{\displaystyle F}{|}}{C}}-O-CH_3.$$
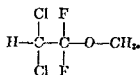
It is a clear, colorless liquid which boils at 104.8°C. at 760 mm. Hg. It freezes at −35°C. It has a latent heat of vaporization of 49 calories per gram. The odor is pleasant and fruity. The compound is stable in the presence of alkalies. The explosive limit at 20°C. is zero. The chemical will not burn at high temperatures, but has a high flash point (145°F.). The vapor density is 3.6 grams per liter. The liquid is miscible with vegetable and animal oils. The water solubility is 2.2 grams per liter. The oil-water distribution coefficient is 400. A 10% concentration gives a distribution of 390 (halothane is 330). The absolute viscosity is 1.070 centapoise at 20°C. and 0.703 at 50°C.

The drug produces general anesthesia when inhaled. Blood concentration in dogs is 140–160 parts per million. It appears to produce anesthesia comparable to ether and chloroform. Elimination appears to be slow.

Little data is available on its pharmacology because the substance is relatively new and has not been studied extensively. The proprietary name is Penthrane.

Halogenated Alcohols

The halogenated aliphatic alcohols are useful anesthetic and sedative drugs. Most important of this group are *trichlor, tribromethanol, ethochlorvinyl* alcohol. The aliphatic halogenated alcohols are not sufficiently volatile for inhalation. Besides they are not inert in the body. Consequently, they are administered either orally, intravenously, or rectally. They are more soluble than the halogenated hydrocarbons and are as a rule less stable. They cannot be prepared by direct halogenation of the alcohol. Usually they are formed by reducing the

halogenated aldehyde or combining a molecule of halogenated hydrocarbon with an aldehyde or ketone.

Trichlorethanol

PREPARATION

Trichlorethanol was first described by Kulz in 1882, but its anesthetic properties were never closely studied. Molitor reinvestigated the pharmacology of the drug in 1937 when the success of tribromethanol called attention to the possibility that the trichlor might also be used as a "basal narcotic." The drug is also called *ethapon*. The usual method of preparation is to reduce chloral in an aqueous solution by the action of yeast in the presence of sugar. Reduction of chloral may also be accomplished by the use of aluminum ethoxide suspended in benzine. The reduction of the aldehyde is expressed by the following equation.

$$Cl-\underset{\underset{Cl}{|}}{\overset{\overset{Cl}{|}}{C}}-\overset{O}{\overset{\|}{C}}-H \overset{+2H}{\longrightarrow} Cl-\underset{\underset{Cl}{|}}{\overset{\overset{Cl}{|}}{C}}-\underset{\underset{H}{|}}{\overset{\overset{H}{|}}{C}}-OH.$$
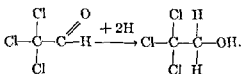
PROPERTIES

Trichlorethanol is a colorless, somewhat viscous liquid, possessing an ethereal odor. The drug is heavier than water (S.G. 1.55 at 20°C.) One ml. contains 1550 mgm. at 20°C. The liquid decomposes if boiled at atmospheric pressure. At reduced pressure, −737 mm. Hg, it distills over at 151°C. unchanged. Solidification to a white powder occurs at 19°C. One part trichlorethanol dissolves in 12 parts of water at 25°C. The liquid is extremely hygroscopic and abstracts water from moist air. The substance is miscible with ether and other organic solvents.

STABILITY

A 5% aqueous solution is slightly acid (pH 5.9). The solution becomes more acid if allowed to stand any length of time. If a solution stands over night the pH falls to 5.5. Aqueous solutions are germicidal. Heat, light, and air cause the pure drug and its aqueous solutions to deteriorate. The usual products of decomposition are chloracetic, trichlorethyl, oxyacetic, and formic acids. Oxidation converts the alcohol to trichloracetic acid. Congo red may be used to detect deterioration, as in the case of "avertin fluid," since the products are acids. The drug is detoxified by the liver, probably by conjugation with glucuronic acid. The kidney excretes the inactivated product which is not hypnotic. Trichlorethanol possesses pharmacological properties which are in many respects similar to tribromethanol. Administration is by rectum, as is the case with tribromethanol. Trichlorethanol was not as widely employed as tribromethanol. The drug is now obsolete.

Tribromethanol (Avertin)

PREPARATION

Tribromethanol was first synthesized by Willstatter in 1923. For a number of years it was the most important halogenated alcohol in current use. It was introduced as an anesthetic drug for surgery by Duisberg in 1926. In Europe it is also known as *ethobrom*. The drug is obtained indirectly by reducing tribromacetaldehyde with the aid of aluminum ethoxide in absolute alcohol in an atmosphere of nitrogen. It cannot be prepared by direct halogenation of ethyl alcohol. The reaction product is then treated with aqueous sulphuric acid and the drug separated. The reaction is expressed by the following equation:

$$\begin{array}{ccc} \text{Br} & \text{O} & \text{Br} \ \text{H} \\ | & \| & \quad\quad | \ \ | \\ \text{Br}\!-\!\text{C}\!-\!\text{C}\!-\!\text{H} + \xrightarrow{2\text{H}} \text{Br}\!-\!\text{C}\!-\!\text{C}\!-\!\text{OH.} \\ | & & \quad | \ \ | \\ \text{Br} & & \text{Br} \ \text{H} \end{array}$$
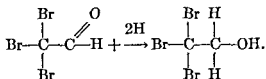
PROPERTIES

Tribromethanol is a white crystalline substance possessing an ethereal odor. The solid melts at 79° to 80°C. with decomposition. Decomposition begins at 70°C. and proceeds slowly since the compound is not heat stable even below the melting point. The liquid boils at 92° to 93°C. at a reduced pressure (10 mm. Hg).

SOLUBILITY

Tribromethanol is only moderately soluble in water. One part dissolves in 40 parts of water at 40°C. The substance is readily soluble in alcohol, ether, benzene, amylene hydrate and other organic solvents. The property of being highly soluble in amylene hydrate (tertiary amyl alcohol) is utilized for storage and shipment of the drug for clinical use. A solution of tribromethanol dissolved in amylene hydrate is marketed as "avertin fluid." Avertin fluid is usually prepared so that 1 gram of crystals is dissolved in ½ gram of amylene hydrate. This mixture results in 1 ml. of solution. Therefore, 1 ml. is the equivalent of 1 gram of the drug. In this form the drug is easily dispensed and stored.

Aqueous solutions of 2½% to 3% strength at 37°C. are used for administration by rectum for basal narcosis. Avertin fluid sinks in water since its specific gravity is 1.4. Pure amylene hydrate floats on water. Complete solution of the combination is necessary for satisfactory results. It can only be obtained by thoroughly shaking the mixture. The drug dissolves slowly, particularly in cold

water. Solutions of avertin fluid should be freshly prepared since they are not stable and decompose upon standing. Dibromvinyl alcohol, tribromacetaldehyde, and hydrobromic acid form when tribromethanol deteriorates:

$$CBr_3CH_2OH \rightarrow Br-\overset{\overset{\displaystyle Br}{|}}{C}=\overset{\overset{\displaystyle H}{|}}{C}-OH + HBr$$

$$CBr_3-CH_2OH+O_2 \rightarrow Br-\overset{\overset{\displaystyle Br}{|}}{\underset{\underset{\displaystyle Br}{|}}{C}}-\overset{\overset{\displaystyle O}{\|}}{C}-H + H_2O.$$
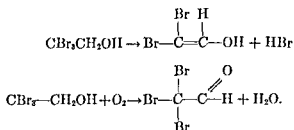
These aldehydes and acids irritate tissues and cause proctitis and even sloughing of the mucosa of the rectum. The rate of decomposition increases as the temperature rises. Thus, at 42°C., the decomposition in aqueous solutions is 50% of that at 70°C. over the same time interval. Distilled water must always be used in preparation of solutions of trichlorethanol or avertin. Traces of alkalies may cause decomposition of the compound. The use of tap water is not advised, particularly in localities where the water is hard. Hardness may be due to alkaline substances, such as bicarbonates, which may cause deterioration. Ultra-violet light causes rapid decomposition of aqueous solutions of tribromethanol, also. Solutions should be used immediately after preparation and discarded if they stand any length of time. Solutions should be tested routinely immediately after preparation for the presence of acid.

DETECTION OF IMPURITIES

The simplest clinical test consists of adding a drop of 0.01% Congo red (sodium salt) dissolved in water. The dye possesses a purple color below a pH of 3 (acid form) and a pink color at a pH

of 5 or above (sodium salt). Decomposition of tribromethanol produces hydrobromic acid which causes Congo red to change to a purple color from its usual pink. The test solution may be placed in a test tube, compared with pure water and an equal amount of indicator. Objection has been raised to the low pH range in which Congo red changes color. To obviate this, indicators with a higher range have been suggested. Bromcresol purple, which changes color in the pH range from 5 to 6.8, has been used by some clinicians because of greater sensitivity. A "universal" indicator, which is a mixture of a number of indicators, possesses different colors at different parts of the pH scale. The British anesthetists have used this indicator because it conveys a more exact idea of the pH of the solution. One must remember in using these more sensitive indicators that "pure" distilled water is not neutral but usually has a pH of 6.4 to 6.8 due to the carbonic acid from dissolved carbon dioxide from the air. One must also remember these tests merely express the hydrogen ion concentrations of the solution and do not detect any particular impurity. Decomposition in solutions with contaminated alkali might easily pass unnoticed since the hydrobromic acid would be neutralized by the alkali and the indicator would not change color. One can see, therefore, the necessity of

using pure water, clean vessels, and carefully controlling the temperature.

ASSAY FOR PURITY

Tests which are specific can be applied to detect decomposition but are too complicated to be employed clinically. Silver nitrate acidified with concentrated nitric acid (1 ml.) may be added to 5 ml. of 3% tribromethanol solution to detect free hydrobromic acid or other uncombined halides. A yellow precipitate forms. Pure solutions of tribromethanol do not respond to this test. Aldehydes (dibromacetaldehyde) may be detected by adding 1 ml. of 10% phenyl hydrazine acetate to 5 cc. of the solution. Sulphates may be detected according to the usual methods (see tests). Amylene hydrate does not interfere with the Congo red or other tests.

DISTRIBUTION IN TISSUES

Tribromethanol is absorbed rapidly from the colon and small bowel. The absorption from the small intestine is more rapid than from the large, but little if any of the solution passes the ileocecal valve following rectal administration. The narcotic effect depends more upon the rapidity of absorption rather than upon the final quantity absorbed. The rate of absorption varies, but usually approximately 50% of a 3% solution, rectally administered, is absorbed within the first ten minutes; 95% within 25 minutes. The maximum blood concentration required for narcosis in man ranges from 6 mgm. to 9 mgm. per 100 ml. of blood. Consciousness is regained when the blood level falls to 2 mgm. to 3 mgm. per 100 ml. Twenty minutes after ingestion of the drug, the brain concentration is double the blood concentration. The drug disappears slowly from lipoid tissue. Brain contains 7 mgm. per 100 gm. of tissue (rabbit) even when the animal is conscious and none can be detected in the blood.

DETOXIFICATION

Tribromethanol is detoxified by the liver by conjugation with glucuronic acid. In perfusion experiments, the blood concentration can be reduced from 130 mgm. per 100 ml. to 6 mgm. in 30 minutes. The conjugated product is believed to be similar to that formed between chloral and glucuronic acid, but its exact structure has not been definitely established. The rate of detoxification in the intact animal varies. Evidence exists that most of the drug is eliminated within four hours. Traces may appear in the urine for as long as 48 hours. The drug is non-volatile so that excretion through the lungs does not occur. Bromine-containing substances have been detected in perspiration following tribromethanol administration suggesting that there is some excretion through the skin.

ISOPRAL

Isopral, or trichloroisopropyl alcohol, possesses hypnotic properties, but is little employed in therapeutics. The substance is a white crystalline substance with a pungent taste and camphor-like odor which melts at 50°C and boils at 161° to 162°C. One part is soluble in 35 parts of water. It sublimes at ordinary temperatures. It is obsolete and not presently used.

Chlorobutanol

PREPARATION

Chlorobutanol or chloretone is an important tertiary halogenated alcohol. Other names for it are methaform, chlorobutol, and acetone-chloroform.

hyde is less stable than the hydrate and polymerizes more freely.

If chloral and chloral hydrate are heated with sodium, potassium and other hydroxides, *chloroform* and an organic salt form. If sodium hydroxide is used, sodium formate and chloroform result; if calcium hydroxide is used, calcium acetate and chloroform result. It was once thought that the hypnotic effect of chloral was due to the decomposition of chloral to chloroform in the tissues. No evidence exists to support this contention. Chloral forms during the metabolism of trichlorethylene. Chloral is reduced to trichlorethanol, a powerful hypnotic, by treatment with hydrogen and a catalyst. The reduction is usually accomplished by the use of aluminum ethoxide in alcohol. Chloral and chloral hydrate are oxidized by nitric acid to trichloracetic acid. This acid is irritating

$$CCl_3CHO + NH_3 \rightarrow CCl_3-\underset{\underset{H}{|}}{\overset{\overset{OH}{|}}{C}}-NH_2.$$
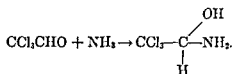
Chloral ammonia is an addition product which, like chloral, possesses hypnotic properties. Chloral ammonia, when heated over a water bath, loses one molecule of water to form *chloralimide* or trichlorethylidene amide:

$$CCl_3-\underset{\underset{}{|}}{\overset{\overset{H}{|}}{C}}-NH.$$
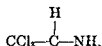
Reduction of chloral by ammoniacal silver solutions is similar to that of other aldehyde derivatives. A precipitate of silver results. Chloral may react with urethane to form *chloral urethane* which is often called *uralium*, *ural*, or *uraline*. Chloral also reacts with other amides, such as formamide, to form *chloral formamide*:

$$CCl_3CHO + H-\overset{\overset{O}{||}}{C}-NH_2 \rightarrow CCl_3-\underset{\underset{H}{|}}{\overset{\overset{OH}{|}}{C}}-\underset{\underset{H}{|}}{N}-\overset{\overset{O}{/\!\!/}}{C}-H.$$
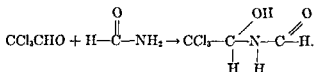
to tissues and possesses no value as a hypnotic drug.

CONDENSATION PRODUCTS

The aldehyde group of chloral reacts,

$$CCl_3CHO + 2C_2H_5OH \rightarrow CCl_3-\underset{\underset{H}{|}}{\overset{\overset{O-C_2H_5}{|}}{C}}-O-C_2H_5 + H_2O.$$

as do other aldehydes, to form aldehyde ammonia, hydrazines, and oximes. If ammonia is passed into a chloroform solution of chloral, *chloral ammonia* forms:

Halogenated aldehydes interact with alcohols to form acetals in the same manner as do the non-halogenated aldehydes. Ethyl alcohol forms the alcoholate which is represented by the following structure:

Chloral alcoholate. is less potent than chloral itself. Conjugation of chloral with amylene hydrate results in Dormiol. The compound has been conjugated with mephanesin (Tolserol) to form *chloral-*

mephanesin. Chloral also forms conjugates with pentoses and hexoses. Conjugation with arabinose gives rise to arabinose-chloralose and conjugation with erythritol gives rise to *penta-erythritol-chloral* or petrichloral. This compound is a hypnotic and sedative with pharmacological properties similar to chloral. The proprietary name is *Perichlor.* Glucose reacts with chloral to form *glucochloral* or *chloralose.* Choralose is an important hypnotic used for anesthesia in laboratory animals and is described subsequently. If chloral is mixed with an equivalent amount of camphor, *chloral-camphor* forms. Chloral may also be condensed with antipyrine and with phenol to form compounds which are used for topical anesthesia.

Chloral, chloral hydrate, and all the forementioned products derived by condensation or mixing chloral with other substances are solids or liquids with high boiling points. None is sufficiently volatile to be of any value as an inhalation anesthetic agent.

DETOXIFICATION

Chloral hydrate, as well as chloral, is rapidly detoxified in the body. Although traces are eliminated unchanged in the urine, the greater portion of an ingested therapeutic dose of the drug is eliminated as *urochloralic acid.* The latter compound is believed to be a glucoside resulting from conjugation of chloral with glucuronic acid by the liver. The exact structure of urochloralic acid has not been definitely established. The acid may be recovered from urine as white, silky, colorless needles which melt at 142°C. The crystals are soluble in water, alcohol, and other organic solvents. Solutions of urochloralic acid reduce alkaline copper solutions used to test for urinary glucose. In cases of coma, from overdosage of the drug, a positive response to reduction tests may be misinterpreted and the reducing substance may be mistaken for glucose.

IDENTIFICATION

Chloral responds to the usual tests for aldehydes. A few drops of a saturated solution of phloroglucinol and 1 ml. of a 20% sodium carbonate solution produce a brick red color if chloral is present. Inasmuch as alkalies convert chloral to chloroform and formates, tests for chloroform requiring alkaline solutions may be positive if chloral is present. Nessler's reagent produces a precipitate with chloral which is not obtained with chloroform.

Toxicological specimens suspected of containing chloral or its derivatives must be analyzed promptly; otherwise decomposition to chloroform may occur and a negative response may be obtained.

Chloral-urethane

This substance is often referred to as uralium, ural, or uraline. It possesses analgesic properties. It is obtained by the interaction of chloral and urethane in the presence of hydrochloric acid. It is a white, crystalline powder which melts at 103°C.

Chloralose

PREPARATION

Chloralose is an important substance, widely employed for anesthesia in animal experiments in laboratories. Chloralose or glucochloral, as it is also called, is a condensation product of chloral and glucose. The drug is prepared by heating equal parts of anhydrous glucose and anhydrous chloral on a water bath. Chloralose possesses two isomers, α

chloralose and β chloralose. The α chloralose is the isomer which is used for hypnosis and anesthesia. Both the α and δ derivatives form during the reaction. The formation of one or the other can be influenced by temperature and hydrogen ion concentration. Beta chloralose is also known as *parachloralose*. Beta chloralose possesses no narcotic properties and may cause convulsions.

PROPERTIES

Alpha chloralose is a white crystalline substance with a disagreeable, bitter taste. It melts at 185°C. Beta chloralose melts at 210°C. One part of α chloralose is soluble in 175 parts of cold water. The substance is very soluble in alcohol, ether, and other organic substances. Both the α and δ forms possess the empirical formula ($C_6H_{10}O_6.CCl_3CHO$) and molecular weight of 309.46. Chloraloses were first described by Hefter in 1899.

BROMAL

Bromal, or tribromacetaldehyde, is made by passing bromine vapor into cold absolute alcohol. The reaction is similar to that which occurs when chloral forms from chlorine and alcohol. Bromal,

like chloral, is an oily liquid which forms bromal hydrate when mixed with water. Bromal hydrate, like chloral hydrate, is a solid substance. Bromal boils at 174°C. and easily decomposes. Bromal hydrate melts at from 53° to 54°C. The drug is very soluble in water, alcohols, chloroform, and other organic solvents. It is more toxic, less potent, and less stable than chloral hydrate.

Mixtures of Halogenated Derivatives

Various mixtures of halogenated hydrocarbons have been used for inhalation anesthesia, particularly in Europe. Such mixtures are now obsolete and seldom used. Among the most prominent were:

Anesthol	Parts (%)
Ethyl chloride	17
Chloroform	35
Ethyl ether	47

Somnoform	
Methyl chloride	60
Ethyl bromide	5
Ethyl chloride	35

Alkaform (A C.E. mixture)	
Alcohol	16
Chloroform	34
Ethyl ether	50

Introduction to Non-aliphatic Compounds

AROMATIC, HETEROCYCLIC AND NITROGEN CONTAINING COMPOUNDS

CHEMICAL CLASSIFICATION VERSUS PHARMACOLOGIC

THE GROUPING of central nervous system depressants into chemical types does not coincide with groupings arranged according to pharmacologic actions. Classification of depressants as aliphatic, non-aliphatic, cyclic, heterocyclic and so on results in some degree of overlapping between chemical characteristics and pharmacological activity. The often made division of central depressants into volatile and non-volatile drugs has some merit from a pharmacologic standpoint but ignores chemical classification entirely. The volatile anesthetics are "complete" anesthetics and abolish reflex activity in therapeutic dosages. Non-volatile drugs as a rule are hypnotic and partially analgesic and are not completely anesthetic in usual doses. Some liquids, notably the alcohols and aldehydes, are volatile but are included among the non-volatile drugs because they behave pharmacologically like non-volatile compounds. The emphasis in this text is on the chemical nature of these drugs. Therefore, the chemical grouping is the one which is used for classification.

ALIPHATIC VERSUS NON-ALIPHATIC COMPOUNDS

The discussion in previous chapters has dealt largely with aliphatic and to a lesser extent with alicyclic compounds. The hydrocarbons, alcohols, aldehydes, ethers, esters and their halogenated counterparts have been discussed among these. Thus, compounds consisting of carbon chains with hydrogen, oxygen and the halogens have been considered. The ensuing discussion deals with cyclic compounds of the aromatic and heterocyclic type, with compounds containing nitrogen and with compounds containing sulphur and other elements. The benzene ring, unimportant in inhalation anesthetics, assumes an important role in the compounds to be discussed. Nitrogen, which has not appeared in compounds discussed heretofore, becomes prominent either as part of the ring or in the side chains. Sulphur, likewise, appears in the ring or in the side chain of some of the compounds to be discussed.

Most hypnotics, all narcotics, the narcotic antagonists, the analeptics, the autonomic drugs, the local anesthetics and the neuromuscular blocking agents are non-aliphatic derivatives. The molecular structures of these compounds are usually more complex than those of the comparatively simple and low molecular weight aliphatic substances. Many of the non-aliphatic drugs are obtained from plant or animal sources. The majority, however, are prepared synthetically. Many of the synthetic substances have chemical structures, except for mi-

nor variations, similar to naturally occurring compounds. However, minor variations often enhance or attenuate desired physiological effects or cause increases or decreases in toxicity. For example, local anesthetics have been synthesized similar in structure to cocaine.

Some of these are less toxic or have a more intense anesthetic action. Minor changes in chemical structure frequently convert compounds which are physiologically active to compounds which are inactive or toxic.

THE ROLE OF NITROGEN IN NON-ALIPHATIC COMPOUNDS

AMINES

Nitrogen appears in most compounds related to anesthesia as an amino group (valence 3) or as a quaternary ammonium group (valence 5). In both cases the nitrogen confers basic properties to the compound. Nitrogen also appears in compounds which are not basic, as in the pyrimidine ring of the barbiturates, in the purines, in the ureas and the carbamates. These derivatives are described in subsequent chapters. The amines may be considered as ammonia with one or more hydrogen atoms replaced by an organic radical. The radical may be derived from aliphatic, alicyclic, aromatic, or heterocyclic structures. Replacement of one hydrogen of ammonia by a radical results in a primary amine, replacement of two in a secondary amine and of three in a tertiary amine:

$$H-\overset{\underset{\displaystyle |}{H}}{N}-H \qquad R_1-\overset{\underset{\displaystyle |}{H}}{N}-H$$

$$R_1-\overset{\underset{\displaystyle |}{R_3}}{N}-R_2 \qquad R_1-\overset{\underset{\displaystyle |}{R_2}}{N}-R_3$$

All three types of amines are basic. Tertiary amines are usually more basic than secondary or primary. The amino group also confers hydrophilic properties to a molecule. In other words, it tends to make a compound water soluble. The amino nitrogen may appear as a side chain or it may be an integral part of a

heterocyclic ring structure. If it is part of a heterocyclic structure it gives rise to compounds which are secondary or tertiary amines, depending upon whether or not a hydrogen atom or an organic radical occupies the third valence of the nitrogen. If the valence is satisfied by a hydrogen atom a secondary amine forms; if by an organic radical the compound is a tertiary amine:

$$\langle\ \rangle\!\!N-H \qquad \langle\ \rangle\!\!N-CH_3.$$
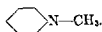
When an amino group replaces a hydrogen atom attached to a carbon in an aliphatic compound an *aliphatic* amine forms, when it replaces a hydrogen atom of a benzene ring an *aromatic* amine forms, when it is placed on a heterocyclic structure a *heterocyclic* amine forms. These amines likewise are all basic.

The amino group may also replace a hydroxyl group of the carboxyl radical of carboxylic acid to form an amide:

$$R-\overset{\underset{\displaystyle \|}{O}}{C}-OH \qquad R-\overset{\underset{\displaystyle \|}{O}}{C}-NH_2$$

Many substituted amides are known some of which are hypnotic. These are described in subsequent chapters. Nitrogen in the amines is trivalent. Amines, like ammonia, form salts with acids:

$$NH_3 + HCl \rightarrow NH_4Cl$$

$$RNH_2 + HCl \rightarrow RNH_3Cl$$
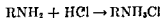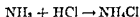
QUATERNARY BASES

The nitrogen may also be pentavalent in which case the compounds are referred to as quaternary bases. These are actually ammonium hydroxide in which the hydrogen atoms have been replaced by organic radicals. Quaternary bases are discussed in Chapter 23. Amines form important groupings in narcotics, local anesthetics, sympathomimetic and anticholinergic compounds. Quaternary bases are important in the structural configuration of muscle relaxants, ganglionic blocking agents, and cholinergic compounds.

THE ALKALOIDS AND VEGETABLE BASES

The word "alkaloid" means resembling alkalies or alkali-like. The term was once used in a general sense to include all nitrogen containing compounds of plant origin. These substances were also referred to, incorrectly, as *vegetable bases*. The term *vegetable bases* is reserved principally for the open-chain class of amines and quaternary bases derived from plant sources. Compounds of the choline type are vegetable bases.

Studies of the structures of alkaloids lead to their synthesis or to synthesis of compounds of similar molecular configuration and pharmacologic behavior. As a result, alkaloids have become less important in therapeutics. Numerous compounds are now available which are similar structurally and pharmacologically to naturally occurring alkaloids. Many alkaloids are now being synthesized and are no longer obtained from natural sources. Most of the ephedrine used today, for example, is prepared synthetically instead of being obtained from its natural source, Ma Huang.

ALKALINE PROPERTIES OF ALKALOIDS

Alkaloids form salts with acids since they are basic in nature by virtue of their amino and quaternary nitrogen atoms. The nitrogen atoms, particularly in the heterocyclic compounds, most often are present in the form of *tertiary amines*. In some heterocyclic structures the nitrogen atom in the ring may be linked by a double bond to one adjacent carbon atom and by a single bond with the other adjacent carbon atom. Such a compound behaves as a tertiary amine:

$$-\overset{\displaystyle |}{\underset{\displaystyle |}{C}} \\ -\overset{\displaystyle |}{C} = N.$$

COMPLEX NATURE OF ALKALOIDS

The simplest alkaloids contain hydrogen and carbon and nitrogen. Practically all alkaloids contain oxygen in addition to carbon, hydrogen and nitrogen. Nicotine is an exception. Oxygen and sulphur may also be present in the rings, but are not commonly found there. As a rule, the molecules of alkaloids are large and complex with numerous heterocyclic structures. The heterocyclic group is often combined with aromatic groups, as is the case with morphine, papaverine, quinine and so on. Although numerous heterocyclic structures have been identified in alkaloids those most frequently encountered are derived from *pyridine* and *quinoline*. Pyridine may be considered as a benzene ring with one carbon atom replaced by one nitrogen atom,

The pyridine ring gives rise to many of the simpler alkaloids. Two benzene rings join together to form naphthalene,

an aromatic hydrocarbon. When a pyridine ring is fused with a benzene ring quinoline forms. Quinoline is an important heterocyclic structure,

A number of local anesthetic drugs, quinine and papaverine are derived from quinoline. Pyridine is not fully saturated. When pyridine is fully hydrogenated piperidine forms which is represented as follows:
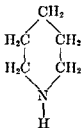
Piperidine is the essential ring structure about which the synthetic narcotics, such as meperidine (Demerol) are formed. The five-membered ring contains one nitrogen and four carbon atoms is known as pyrrole,
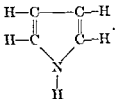
In this structure, the nitrogen carries a hydrogen atom. All its valences, therefore, are satisfied. The compound, therefore, is a secondary amine and responds to all tests for such an amine. The nitrogen atom of pyridine has a valence of three, one of which is satisfied by a single carbon atom and the other two by a double bond shared by an adjoining car-

bon atom. The compound is similar to and behaves like a tertiary amine.

The pyrrole ring may be fused with a benzene ring to form *indole*, a substance important in biology. Cyclic structures containing more than one nitrogen atom, such as *pyrazole*, are known. Frequently, in alkaloids, two or more rings are fused in such a manner that nitrogen is common to both rings. Ecgonine, the alcoholic portion of the cocaine molecule, is a heterocyclic structure resulting from the fusion of a five-membered pyrrole ring with a six-membered pyridine ring. The nitrogen atom is common to both cyclic structures. Similar configurations are present in atropine and scopolamine. These structures and other heterocyclic structures will be presented as the discussion of the individual alkaloids is unfolded in the ensuing chapters.

EFFECT OF SIDE CHAINS ON REACTIVITY OF ALKALOIDS

Side chains of different types may be attached to individual carbon or nitrogen atoms of the molecule of the alkaloid. These side chains may be reactive groups, such as the hydroxyl, carboxyl, aldehyde, ketone and so on. These groups impart reactions characteristic of their group to the compound. The amino group may be substituted and add additional nitrogen and, therefore, additional basicity to the compound. Alkaloids containing such groups may undergo oxidation, acetylation, hydrolysis, halogenation, reduction and various other reactions. Alkaloids, therefore, can be classed as aldehydes, alcohols, acids, ethers, esters, and other types, depending upon the groups present. Morphine, for example, contains two hydroxyl groups, one of which is a phenolic hydroxyl. It, therefore, behaves as a

phenol. The other hydroxyl group is an alicyclic one and, therefore, confers properties of a secondary alcohol to morphine. Morphine also contains a tertiary amino nitrogen and an ether linkage. It may, therefore, be an amine, a phenol, an ether and a secondary alcohol.

ROLE OF ALKALOIDS IN PLANTS

A given plant source yields, as a rule, several alkaloids. Opium, for example, yields several dozen. It is unusual to find only one alkaloid in a given plant source. Alkaloids in a given plant are usually related both chemically and pharmacologically. Codeine and morphine, for example, are chemically and pharmacologically related. The purposes of alkaloids in plants are not known. Any thoughts which have been expressed are merely speculative. Possibly they are toxic substances intended to protect the plant from animals who would eat them. Possibly they are waste products or they may be chemical messengers whose role in the plant is similar to that of hormones in the animal body.

In a strict sense a drug is not an alkaloid unless it is derived from a plant. Many compounds are known which possess molecular configuration and reactivity similar to alkaloids. Synthetic compounds similar to alkaloids are referred to as alkaloids. However, they cannot be rightfully classed as alkaloids. The term therefore is now generally misused. As time passes alkaloids will have less and less importance in the field of therapeutics, since they will be synthetic for the most part.

Most alkaloids manifest high degrees of physiological activity or toxicity in doses which are relatively minute compared to the therapeutic doses of aliphatic anesthetics. The majority are highly poisonous when given in excess.

CHEMICAL AND PHYSICAL PROPERTIES

Alkaloids possess certain distinctive chemical and physical properties. Most alkaloids are bitter, colorless, white solids. An alkaloid exists in two forms— as a *free* or *basic form* or as a salt of a mineral or organic acid. Aqueous solutions of the free alkaloid are alkaline. The pH varies with the nature of the compound. The salts, particularly those formed from strong acids, have an acid reaction since they are formed from a weak base and a strong acid. In the formation of the salt with certain acids the hydrogen of the acid is incorporated into the compound. The reaction is not a neutralization in the strict sense of the word, particularly in the absence of water.

$$RNH_2 + HCl \rightarrow RNH \cdot HCl.$$
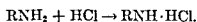
The salt formation of alkaloids, since they are amines, is similar to the union of ammonia with an acid to form ammonium salts. When hydrochloric acid is used to form the salts the resulting compounds are referred to as hydrochlorides.

$NH_3 + HCl$	$NH_4 \cdot HCl$	(NH_4Cl)
$RNH_2 + HCl$	$RNH_2 \cdot HCl$	(RNH_2Cl)
$R_2NH + HCl$	$R_2NH \cdot HCl$	(R_2NH_2Cl)
$R_3N + HCl$	$R_3N \cdot HCl$	(R_3NHCl)
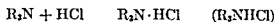
Alkaloids are found as the salts of organic acids which are normally present in their respective plant sources. Among the more common acids in plants which form naturally occurring salts are malic, lactic, citric, sulphuric, benzoic and acetic. The extracted alkaloids are purified and converted to and dispensed as salts of mineral acids such as hydro-

chloric, sulphuric, hydrochloric and so on. Organic acids are sometimes used when the salts of mineral acids are insoluble or unstable. The free alkaloid is less soluble in water than the salt. The free base is precipitated from aqueous solutions of salts by the hydroxides of potassium, sodium, or barium. In some cases weak bases, such as ammonium hydroxide, or alkaline metal carbonates and bicarbonates liberate the free base also. Free bases are usually oily liquids or white solids. As is the case with most amines, they possess varying degrees of volatility. They precipitated free bases redissolve and form salts when acids are added. The free bases are soluble in organic solvents—ether, benzene, chloroform, acetone and so on. Salts are generally less soluble or insoluble in these substances. As a rule, the free base is less stable than the salt. Some alkaloids decompose when exposed to light or heat. Amines, ammonia, hydrocarbons, and other degradation products form as by-products of such decomposition.

OPTICAL ACTIVITY OF ALKALOIDS

Most alkaloids have one or more asymmetric carbon atoms and are, therefore, *optically active* (Chaps. 9, 25). This physical property is directly associated with physiological activity. Naturally occurring alkaloids are usually levorotatory. Dextrorotatory alkaloids are less common than levo. D-turbocurarine is a notable example of a dextrorotatory compound. Certain dextrorotatory compounds have no physiological activity. Dextro tropine tropate, which is a constituent of atropine, is physiologically inactive.

IDENTIFICATION OF ALKALOIDS

The identification of alkaloids is important particularly in toxicology. Alka-

TABLE I.16

Name	Composition
Mayer's Reagent..	Potassium Mercuric Iodide
Dragendorff's Reagent.	Potassium Bismuth Iodide
Hager's Reagent	Picric Acid
Wagner's Reagent.	Potassium Iodide and Iodine
Marme's Reagent	Potassium Cadmium Iodide
Scheibler's Reagent	Phosphotungstic Acid
Sonnenschein's Reagent	Phosphomolybdic Acid Platinum Chloride Potassium Dichromate Silicotungstic Acid Mercuric Chloride Gold Chloride

loids are identified by their melting or boiling points, solubility in various reagents, optical activity precipitating reactions, and color tests, together with reactions and tests for specific groups or side chains. Mineral acids, such as nitric, sulphuric, or hydrochloric, either alone or in combination with oxidizing agents, convert alkaloids to colored compounds. The structure of many of these colored compounds is unknown because they result from dehydration, reduction, oxidation and other changes in the molecule of the alkaloid. Certain mixtures, such as tungstic acid, picric acid, iodine, mercuric salts, and molybdic acid, known as *alkaloidal reagents* (Table I.16) form insoluble salts with alkaloids. The precipitates which appear may form the basis for identification since many are colored or have a distinctive crystalline structure. The color is often specific for a particular alkaloid. Many synthetic substances have molecular configurations similar to alkaloids. They, therefore, react in the same manner as the alkaloids do when mixed with these reagents. These synthetics possess many chemical and physical properties of alkaloids. Local anesthetics, for example, respond to these tests in the same manner as do the alkaloids.

Sulphur-containing Substances: Thioderivatives and Sulphonemethanes

SIMILARITIES BETWEEN OXYGEN AND SULPHUR

SINCE SULPHUR is the element below oxygen in the periodic table its role in organic chemistry is similar to that of oxygen. A series of dicovalent compounds may be formed from sulphur which are analogous to organic oxygen containing compounds. Thus, compounds containing oxygen may have thio counterparts in which an atom of sulphur replaces an atom of oxygen. The prefix *thio* indicates the presence of sulphur in an organic compound combined in this fashion. In addition to the oxygen analogues a number of types of tri and tetra covalent sulphur compounds exist for which there are no oxygen analogues.

THIO COMPOUNDS OF THE ALIPHATIC TYPE

The oxygen atom of the hydroxyl group may be replaced by sulphur to form the SH or *sulphydryl group* which gives rise to thioalcohols, or *mercaptans*. The thioaliphatic alcohols are often called *alkanthiols*. The ethyl thioalcohol (C_2H_5SH) is ethyl mercaptan or ethanthiol. Primary, secondary, and tertiary thioalcohols or mercaptans are possible as is the case with oxygen analogues. The oxygen of the aldehyde group may be replaced in a similar manner with sulphur to form *thioaldehydes*. Likewise,

thioketones

$$R-C-R$$
$$\overset{\|}{S}$$

and *thioethers* (R—S—R), form. Thiocarboxylic acids may also be formed. These are of three types: those in which the oxygen of the hydroxyl group is substituted by sulphur (*thiolic*),

$$\overset{O}{\overset{\|}{R-C-SH}};$$

those in which the hydroxyl remains intact but the oxygen of the carbonyl is replaced by sulphur (*thionic*),

$$\overset{S}{\overset{\|}{R-C-OH}};$$

and those in which all the oxygen atoms are replaced by sulphur (*thionothiolic*),

$$\overset{S}{\overset{\|}{R-C-SH}}.$$

Numerous other replacements occur, as in urea, cyanates, and amides. These are unimportant in this discussion except thiourea which is used in the condensation with *malonic acid* to form thiobarbiturates.

CYCLIC STRUCTURES CONTAINING SULPHUR

Any atom capable of covalent bonding may appear in a cyclic structure. Sul-

335

phur, therefore, may also appear as one or more atoms of a heterocyclic structure. The five membered ring *thiophene*, in which sulphur is joined with four carbons, is one of the simplest sulphur-containing heterocyclic structures. The thiomalonyl urea (see Chap. 19) is a more complex heterocyclic structure. Sulphur may also appear in a ring with another element besides carbon, as for example nitrogen. The thiazane structure from which Dolitrone is derived has four carbon atoms, a sulphur and a nitrogen atom. The phenothiazine structure

containing a sulphur and nitrogen atom gives rise to a series of specific central depressants used as tranquilizers. A thiophanium derivative (Arfonad) contains an atom of sulphur in a four carbon ring.

INORGANIC SULPHUR COMPOUNDS

Sulphur forms an hexafluoride which is a stable, inert compound having a potency less than nitrous oxide in comparable concentrations when inhaled. The oxides of sulphur and the hydride form important acids but neither are important as far as anesthesia is concerned. Organic derivatives of these acids are described in the next paragraph.

DERIVATIVES OF SULPHURIC AND SULPHUROUS ACID

Besides the thio compounds, certain organic compounds are derived from sulphur-containing acids. Sulphur forms ten oxides which are anhydrides of sulphur acids. Suphur dioxide (SO_2) combines with water to form H_2SO_3, or *sulphurous acid*. Sulphur trioxide combines with water to form *sulphuric acid*, H_2SO_4. Sulphur also forms a hydride (H_2S) which in aqueous solution also is an acid. Sulphurous acid and hydrogen sulphide are volatile weak acids which are poorly ionized. Sulphuric acid is a strong highly ionized acid. A molecule of sulphuric acid is composed of one sulphur atom, two hydroxyl groups and two oxygen atoms, structurally represented as follows:

$$HO-\overset{\overset{\displaystyle O}{\|}}{\underset{\underset{\displaystyle O}{\|}}{S}}-OH$$

A hydrogen from an organic compound, as for example a hydrocarbon and a hydroxyl of the acid combine to split out a molecule of water. An HSO_3 group then becomes attached to the molecule to form an organic, *sulphonic acid*. The second hydroxyl group may then be replaced to form a *sulphone*. Sulphonic acid and sulphones are important substances in medicine. Their formation is given at the top of the next page.

Aromatic sulphonic acid derivatives form the basis of numerous chemotherapeutic agents, such as sulphanilamide and other "sulpha" drugs. The reaction for the formation of a sulphone by replacement of the hydrogen atoms of the hydrocarbon occurs readily with aromatic hydrocarbons. The attachment of the sulphone to methane is a more laborious process and cannot be used for the formation of the aliphatic sulphones. When sulphurous acid (H_2SO_3) is substituted for sulphuric, *sulphinic* compounds form.

In summary then, one may say three major groups of organic sulphur com-

$$R-\overset{\overset{\displaystyle H}{|}}{\underset{\underset{\displaystyle H}{|}}{C}}-H + HO-\overset{\overset{\displaystyle O}{\|}}{\underset{\underset{\displaystyle O}{\|}}{S}}-OH \rightarrow R-\overset{\overset{\displaystyle H}{|}}{\underset{\underset{\displaystyle H}{|}}{C}}-\overset{\overset{\displaystyle O}{\|}}{\underset{\underset{\displaystyle O}{\|}}{S}}-OH + H_2O$$

$$R-\overset{\overset{\displaystyle H}{|}}{\underset{\underset{\displaystyle H}{|}}{C}}-\overset{\overset{\displaystyle O}{\|}}{\underset{\underset{\displaystyle O}{\|}}{S}}-OH + H-\overset{\overset{\displaystyle H}{|}}{\underset{\underset{\displaystyle H}{|}}{C}}-R \rightarrow R-\overset{\overset{\displaystyle H}{|}}{\underset{\underset{\displaystyle H}{|}}{C}}-\overset{\overset{\displaystyle O}{\|}}{\underset{\underset{\displaystyle O}{\|}}{S}}-\overset{\overset{\displaystyle H}{|}}{\underset{\underset{\displaystyle H}{|}}{C}}-R + H_2O$$
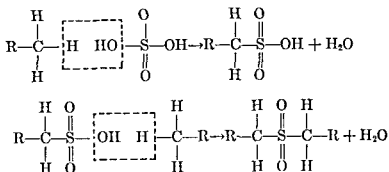
pounds are known: (1) thio compounds, which are the counterpart of oxygen-containing radicals and have the oxygen replaced by sulphur; (2) compounds derived from sulphur-containing acids, such as sulphones, sulphines, sulphates, and sulphites; and (3) heterocyclic compounds in which sulphur appears as one or more of the atom which completes the ring.

SULPHONEMETHANES

A number of aliphatic series derivatives, known as the *sulphonemethanes*, possess hypnotic properties. The sulphonemethanes, now obsolete, were once used extensively for sedation. Sulphonal, trional, and tetronal were the most common drugs of this group. The more efficient and potent drugs, particularly the barbiturates, have superseded them. They are little used in clinical medicine today.

Sulphonal is methane in which two hydrogen atoms are replaced by a sulphonic acid group. Each hydroxyl of the sulphonic acid radical is then replaced by an ethyl radical to form diethyl sulphone methane:

$$\begin{array}{c} CH_3 \qquad SO_2-C_2H_5 \\ \diagdown\;\diagup \\ C \\ \diagup\;\diagdown \\ CH_3 \qquad SO_2-C_2H_5 \end{array}$$
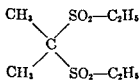
The remaining hydrogen atoms of the methane nucleus are replaced by methyl groups. Thus the compound is actually a diethyl sulphone dimethyl methane. The methylation increases the potency of the drug.

SULPHONAL

Sulphonal was introduced into therapeutics by Baumann and Kast in 1886. It is a white, odorless, and almost tasteless powder composed of crystals which are only slightly soluble in cold water (1 part in 365 at 25°C.), but are very soluble in boiling water (1 part in 16), and moderately soluble in alcohol, ether, and chloroform. It melts at 124° to 125°C. without decomposition. It is volatile with steam. Aqueous solutions are neutral to litmus, as one would expect from its structure, since the acid hydroxyl is replaced by the ethyl group. Absorption from the gastrointestinal tract is poor due to its poor water solubility. The drug has cumulative properties and remains unchanged in tissues, particularly after repeated doses. Strong heating decomposes it into carbon, carbon dioxide, water, and sulphur dioxide, along with other miscellaneous carbon compounds, depending upon the temperature employed. Sulphonal sublimes at 60°C. Therapeutic doses are detoxified in the body. The drug is largely excreted as ethyl sulphonic acid, although it may be eliminated unchanged if the

ingested dose is large. Elimination is slow, often requiring several days.

Sulphonal is prepared by condensing ethyl mercaptan with acetone to form the dithioether of acetone:
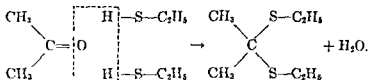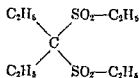
This is oxidized further by potassium permanganate to form sulphonal.
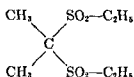
TRIONAL AND TETRONAL

The slow absorption and elimination of this compound prompted a search for more effective related compounds. *Trional*, which is diethyl sulphone ethyl methyl methane, has one more ethyl group than sulphonal. This replaces one of the methyl groups on the methane nucleus in sulphonal:
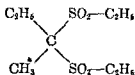
Like sulphonal it is a white powder which melts at 76°C., is bitter and insoluble in water. One part dissolves in 200°C. and 1 in 30 at 100°C. Trional is more easily decomposed in the body than sulphonal. The drug is prepared by condensing the methyl ethyl ketone (acid ethyl mercaptan) and oxidizing the resulting mercaptole as in the preparation of sulphonal. *Tetronal* is similar in action and properties to sulphonal and trional but more potent. Two ethyl groups are present on the methane nucleus.

Its chemical name is diethyl sulphon diethyl methane. Tetronal may be prepared by condensing the diethyl keton with ethyl mercaptan and oxidizing the resulting mercaptole.

Decomposition of sulphonal occurs slowly in toxicological specimens so the substance may be recovered unchanged from tissues post mortem. The drug is easily extracted with organic solvents and the residue is sublimed and identified by appropriate tests. The melting point is used as a confirmatory test for identification. The usual qualitative tests are not specific and a positive reaction may be given by chemically related sulphur substances. Aliphatic sulphones if heated with iron are converted to mercaptan. Sulphonal is converted by ethyl mercaptan which can be identified by its disagreeable odor. A residue of ferrous sulphide remains which may be identified by the characteristic odor of hydrogen sulphide when allowed to react with mineral acids. Heating sulphone methanes with potassium cyanide forms ethyl mercaptan and potassium thiocyanate (KCNS). The latter may be identified by an intense red color when ferric chloride is added to the solution. Sulphides form when sulphones are fused with metallic sodium. The drug is resistant to treatment with halogens, halogen acids, cold concentrated alkalies, nitric or sulphuric acids.

Narcotics: Opium Alkaloids and Synthetic Narcotic Analgesics

ANALGESIC ACTION OF NARCOTICS

A NARCOTIC, according to the classical textbook definition, is a substance which exerts a combined analgesic and hypnotic action. The depressant action on the nervous system is a dual one. The analgesic activity is accomplished not only by an elevation of the pain threshold in the thalamic nuclei but also by altering the psychological response to pain. The pain may not be completely obtunded but the subject is indifferent to it. The non-narcotic analgesics, such as phenacetin and acetyl salicyclic acid, are devoid of this latter action.

Source

For many years the opium alkaloids were the only available narcotic substances. After the chemical structure for morphine was established the chemical groupings responsible for narcotic activity were determined. Numerous compounds, whose structures are patterned after that of morphine, were prepared. These have been referred to as the morphinoids due to similarities of their structure to morphine. The discovery of the analgesic activity of meperidine and methadon by German chemists and pharmacologists led to further studies on relationship of analgesic activity to molecular configuration and the correla- tion of their structure and activity with those of morphine. As a consequence numerous non-morphinoid compounds were prepared. However, for each compound which has proved to be a successful analgesic, hundreds of closely allied compounds in the same series have been prepared which are devoid of narcotic action or are undesirable in some respect. The literature on narcotics is voluminous and a detailed comprehensive discussion of the subject is beyond the scope of this book. The search for the ideal narcotic, one which is truly analgesic, non-addicting and devoid of side actions, goes on. The discussion in this chapter is concerned chiefly with the narcotics obtained from opium and the clinically useful synthetic drugs.

OPIUM
Source

Opium is a complex mixture of plant origin containing over two dozen alkaloids together with various extractives. Opium is derived from the poppy (generic name, Papaver somniferum), a semitropical plant which is cultivated in many parts of the world, but particularly in India, China, Russia, and Middle East areas. The alkaloids account for twenty per cent of the total weight of the crude drug. Many varieties of poppy exist but not all yield narcotic alkaloids. The yield of alkaloids, even in the opium-bearing

poppy, varies widely and is dependent upon the cultivation, climate, time of harvesting, and other factors. After the blossom opens and the petals are lost a capsule containing the seeds forms which ripen in a period of nine to fifteen days. The opium is contained in the wall of the pod. The seeds contain no alkaloids. The opium is harvested from the unripe capsule at the time believed most opportune by an experienced worker. A circular incision is carefully made in the surface so that the pod is not penetrated. A white, resinous exudate oozes from the incision and coagulates into a thick gum. The incision is made late in the day so that the exudate may dry overnight. The thick gum which forms is collected the following morning and is rolled into crude opium balls. The *crude opium* is essentially a mixture of *pectin, waxes, complex sugars,* and *alkaloids* in the form of salts of sulphuric, lactic, or acetic acids. The opium is dried and ground to a powder. In addition, it contains about 10% to 15% water and an acid not found in any other plant, *meconic acid.*

MECONIC ACID

Meconic acid is of interest from a medicolegal standpoint since its identification in toxicological material indicates the presence of opium rather than one of its processed alkaloids. Concentrations of meconic acid run as high as 4% in a specimen of opium. Chemically meconic acid is the dicarboxylic acid of pyrone, a ketone. Meconic acid possesses the following structure:
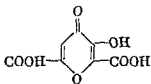
OPIUM PREPARATIONS

Opium powder as such is little used as a therapeutic agent. The official powder (U.S.P.) contains 10% morphine. Tincture of opium is a 10% alcoholic solution of opium. One ml., therefore, contains approximately the equivalent of 1/10 gm of opium which is equivalent to 10 mgm of morphine (1/6 gr.).

The *deodorized tincture* contains approximately equivalent amounts of alkaloid (10%) as the ordinary tincture. The organic non-alkaloidal constituents of crude opium impart a disagreeable taste and odor to the drug. These are removed by extracting the aqueous solution of opium with petroleum benzine or liquid petrolatum. The resulting product is known as the *deodorized tincture of opium.*

A *camphorated tincture* of opium (paregoric) is available. This is a solution of 10% alcohol containing 4 gm. of opium (1/25 the amount in the tincture), 4 gm. of camphor, and 4 ml. of oil of anise per liter.

Granulated opium (U.S.P.) is prepared by drying opium at a temperature not exceeding 26.5°C. and reducing the mass to 16–50 mesh granules. These are then combined with lactose in a proportion to contain 10–15% morphine by weight.

An opium derivative erroneously believed to be devoid of morphine is *pantopon* (also omnopon). Pantopon, frequently referred to as "concentrated opium," is an aqueous solution of all the alkaloids of Turkish opium minus the waxes, resins, meconic acid, and other extractives. The alkaloids are prepared in the form of the hydrochloride salts. One milligram of pantopon is equivalent to 0.6 mgm. of morphine sulphate or 5.0 mgm. opium powder.

The Chemistry of Opium Alkaloids

The opium alkaloids are some of the most useful drugs in therapeutics. As is the case with most alkaloid-bearing plants, the opium plant is the source of a number of alkaloids which are related both chemically and pharmacologically. Although over twenty-five known alkaloids have been identified in opium the clinician uses only several. Table I.18. Chemically the opium alkaloids may be separated into two groups—those derived from the heterocyclic structure, *isoquinoline*, and those derived from the hydrocarbon, *phenanthrene*.

TABLE I 18
THE ALKALOIDS WHICH ARE FOUND IN OPIUM

Morphine	5–15%
Narcotine	2–8%
Codeine.	1–2%
Papaverine	0 5–1%
Thebaine... .	0 15–0 5%
Narceine	0 10–0 4%

Codamine	Neopine
Cotarnine	Papaveramine
Cryptopine	Oxynarcotine
Deuteropine	Porphyrosine
Gnoscopine	Protopine
Hydrocotarnine	Pseudomorphine
Lanthopine	Pseudopapaverine
Laudanine	Rhoeadine
Meconidine	Triptopine
Anarcotine	Xanthaline

Under the general discussion of alkaloids, reference was made to the importance of cyclic structures as a basis for numerous alkaloids. Mention was made of quinoline which is pyridine fused to a benzene ring.

Two quinolines are known, a normal and an isoquinoline. When the nitrogen atom is in position 2

isoquinoline results. This is the ring structure which forms the basis of the isoquiniline group of opium alkaloids. The most important and widely used drug of this group is papaverine. The drug will be discussed further on. The isoquinoline derivatives are non-narcotic.

Phenanthrene derivatives form the basis of the group of narcotics referred to as the *opiates*. In this group are morphine, codeine and thebaine. Phenanthrene is an aromatic hydrocarbon formed by the fusion of the three benzene rings. Phenanthrene is isomeric with anthracene since both these hydrocarbons each contain three benzene rings. In phenanthrene they are fused alternately; in anthracene they occur consecutively.

Phenanthrene, like benzene, has three double bonds in each ring. The hydrocarbon is capable of becoming hydrated, that is, of further hydrogenation. Two rings in morphine are partially hydrogenated. Phenanthrene has no nitrogen. Morphine actually has five rings, two heterocyclic and three hydrocarbon. One heterocyclic contains nitrogen and one oxygen. The nitrogen in morphine forms a tertiary amino group. This, together with two other carbon atoms, forms a bridge between two positions on the phenanthrene ring, or to use a more common and descriptive term, is "hooded on" between two "corners." The nitrogen containing ring is a six-membered heterocyclic ring (Table II.18). An oxygen atom placed between the corners of rings I and III (carbons 4 and 5) forms an ethereal linkage and another six-membered heterocyclic ring (ring IV). The three-ringed phenanthrene is thus converted to a five-ringed structure, two of which are heterocyclic. The nitrogen bears a

TABLE II.18
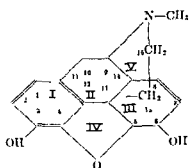
Morphine
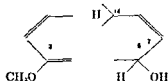
Codeine
(Methyl-Morphine)
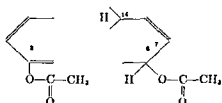
Heroin
(Diacety Morphine)
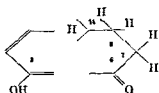
Dilaudid
(Dihydro Morphinone)
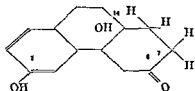
Oxymorphone
(Dihydrohydroxy Morphinone)

(Continued in next column)
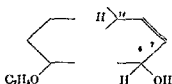
Dionine
(Ethyl Morphine)
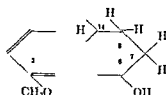
Parecodeine
(Dihydrocodeine)
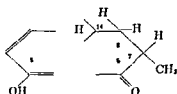
Metopon
(Methyl Dihydromorphinone)
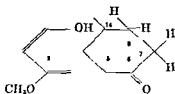
Percodan
(Dihydrohydroxy Codeinone)
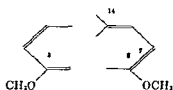
Thebaine
(Dimethyl Morphine)
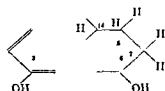
Dihydromorphine
(Paramorphan)
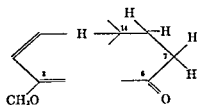
Dicodid
(Methyl Dihydromorphinone)
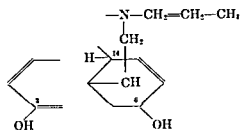
Nalline, Nalorphine
(N-Allyl Nor Morphine)

methyl group. This general structure forms the basis of the opiates and a number of semi-synthetic drugs derived from morphine. One will note that ring I has its double bonds unaltered, and is therefore, aromatic. Rings II and III have some or all their double bonds removed by the addition of hydrogen atoms. Ring III has a single double bond which, when further hydrated, gives rise to metapon, dihydro and morphinone.

IMPORTANCE OF HYDROXYL GROUPS

The carbon atoms in morphine marked 3 and 6 bear hydroxyl groups. Since ring number I is aromatic and not hydrated, the hydroxyl upon carbon 3 is of a *phenolic type*. Morphine, therefore, responds to tests for phenols. Ring III is partly hydrogenated (except carbon 7 and 8). Saturation of the double bonds has occurred and the structure, therefore, is no longer aromatic in nature. Consequently, the hydroxyl on carbon 6 reacts chemically like one on an aliphatic group and confers properties of an *alcohol* to the compound. In this case the

ring is alicyclic and the alcohol is a secondary one. Morphine, then, is a phenanthrene nucleus partially hydrated with a bridge composed of two carbons and a tertiary nitrogen, one phenolic hydroxyl, one alcoholic hydroxyl, and one ether linkage. Morphine responds to the chemical reactions characteristic of these groups. Each group confers a certain type of physiological activity to the compound. The phenolic hydroxyl imparts analgesic, narcotic and central nervous system depressant properties to morphine. The alcoholic hydroxyl is believed to be responsible for tetanizing and convulsive properties. Alterations or substitution of each of the hydroxyl groups change the pharmacological nature of the responses.

Synthetic Derivatives of Morphine

As a rule, the alcoholic hydroxyl is more easily altered than the phenolic. If the hydrogen atom of the phenolic hydroxyl group is replaced by an methyl group, methyl morphine (an ether) or codeine results (Table II.18). This change decreases potency. Codeine has approximately one-fourth the narcotic potency of morphine. The ethyl ether, or dionine, may be formed in a similar manner by replacing the hydrogen atom of the phenolic hydroxyl with an ethyl group. If both the alcoholic and phenolic hydroxyls are methylated, thebaine forms. This has marked convulsant powers.

The hydroxyl groups may be esterified with organic acids. Treating morphine with acetyl chloride acetylates both hydroxyl groups. Diacetyl morphine, or heroin, results. The presence of the acid groups on the phenolic hydroxyl increases narcotic potency. Either hydroxyl group may be oxidized. The phenolic forms a quinone; the alicyclic a ketonic

TABLE III.18

Phenanthrene

Dibenzofuran

Carbazole

Quinoline

Isoquinoline
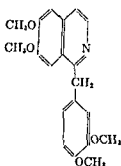
Papaverine
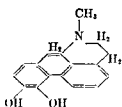
Apomorphine
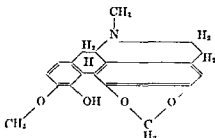
Bulbocapnine

group. Oxidation of the alicyclic hydroxyl group entails the alteration of the ring by further hydrogenation and removal of the single remaining double bond. If the alcoholic hydroxyl in the 6 position is converted to a ketone, dihydromorphinone (Dilaudid) results The masking of free hydroxyl groups diminishes its tetanizing effect and enhances the narcotic effect. Converting the alicyclic hydroxyl to a ketone increases the potency. Dilaudid is approximately ten times more potent than morphine.

the convulsive effect is enhanced if both hydroxyl groups are converted to ethers. Esterification of both hydroxyl groups increases narcotic action. Masking the alcoholic hydroxyl decreases the analgesic effect. Less is known about the effect of altering the phenolic hydroxyl than the alicyclic. The emetic properties of these substances are associated with the presence of the free hydroxyl groups. Masking the hydroxyl groups decreases the emetic properties.

NARCOTIC POTENCY AND STRUCTURAL VARIATIONS OF OPIATES

In general, one may say that the narcotic potency is decreased if the phenolic hydroxyl is converted to an ether and

Naturally Occurring Phenanthrene Opiates

Two phenanthrene derivatives occur in opium in any reasonable quantity— morphine and codeine. Other phenanthrene derivatives available for clinical

use are synthetic or semi-synthetic. Among the semi-synthetic compounds are dionine dihydromorphine, heroin, metopon, oxymorphone (Numorphan), dicodid, dihydrocodeine and so on (Table II.18). These are prepared directly from morphine. They are, therefore, referred to as semisynthetic opiates. Morphine has been synthesized; nonetheless opium still remains the source of the alkaloid and its derivatives.

Synthetic phenanthrene substances have been prepared, best known of which are the morphinan derivatives (Table IV.18). Levorphan (Dromoran) is the most important of these. The levorphan molecule consists of a phenanthrene ring with the six-membered nitro-

gen ring arranged in the same way as in morphine. The six-membered ring bearing the ethereal oxygen is absent. Levorphan is four to five times more potent than morphine.

Structure-Activity Relationships of Narcotics in General

The introduction of the synthetic analgesic narcotics brought out the fact that the phenanthrene nucleus is not essential for narcotic activity and led to reappraisal of the entire subject of relation of molecular configuration to activity. Other cyclic configurations, such as the biphenyl, the piperidines and the oxazolopinediones may appear in compounds which show high degrees of analgesic

TABLE IV.18
MORPHINAN SERIES

Phenanthrene

N-Methyl Morphinan

d, d, l or d Hydroxy Methyl Morphinan
d = Dextrorphan
dl = Racemorphan
l = Levorphan (Dromoran)

Levallorphan
(Hydroxy Allylmorphinan)
(Lorfan)

d, dl, or l Methoxy Morphinan
d = Dextromethmorphinan
dl = Racemethmorphinan
l = Levomethmorphinan
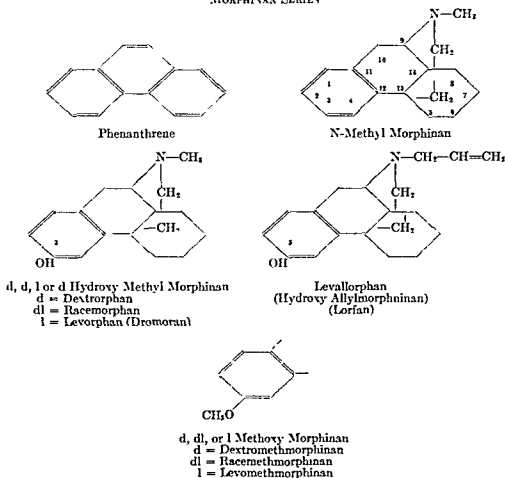
TABLE V.18
BENZMORPHAN SERIES
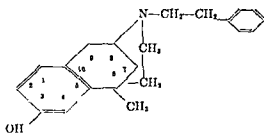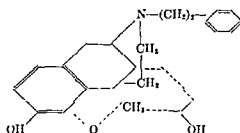
Phenazocine

Phenazocine superimposed on
morphine molecule

activity. Of these newer compounds those derived from piperidine (Table VI.18) are the most extensively used. The molecular configurations appear dissimilar when expressed in the conventional planar manner. However, if visualized in three dimensions similarities in pattern become apparent.

ESSENTIAL GROUPINGS IN NARCOTICS

Three groupings consistently appear to be present in the potent analgesics. These are (1) a prosthetic group consisting of a methyl radical on a tertiary nitrogen atom, (2) one or more oxygen containing prosthetic groups whose distance varies from 7 to 9 angstrom units from the methyl on the nitrogen atom and (3) a bulky blocking portion of the molecule. This blocking moiety is usually a cyclic structure composed of one or more phenyl groups or an isoteric structure. By isoteric is meant that the grouping is similar in molecular shape, molecular weight and electrical activity, and functions in a manner similar to the phenyl group. Eddy indicated that this triad is essentially a quaternary carbon atom connected to a tertiary nitrogen atom by a dimethylene group ($-CH_2CH_2-$) and that this combination is essential for narcotic activity. A quaternary carbon atom has none of its va-

lences satisfied by a hydrogen atom. The quaternary carbon atom in narcotics is centrally located. The quaternary carbon atom must be connected with a phenyl group or another group isoteric with phenyl which serves the same purpose and has the same physical characteristics as the phenyl. This arrangement of groups appears to be essential; nonetheless it cannot unequivocally be the basis for prediction of analgesic action or for preparation of a tailor-made compound of high degrees of activity since all substances which conform to this configuration are not necessarily analgesic. However, all substances which manifest a morphine-like analgesic effect appear to conform to this configuration. The prosthetic or physiologically active groups in narcotics are independent of the general ring structure, since they are found in cyclic structures which are unlike each other and diverse from each other. They are found, for example, on phenanthrene, as in morphine, pipepidine as in meperidine, the biphenyls, the pyridines and so on.

GROUPS RESULTING IN AUTONOMIC AND OTHER ACTIVITIES

The prosthetic groups are similar to those of the atropine-like compounds in many cases, so that some analgesics have a spasmolytic activity and in other cases

compounds have parasympathetic, or sympathetic and even local anesthetic activity. Schuler has proposed that both sympathetic and parasympathetic moieties are present on the narcotic molecule with the single nitrogen atom common to both. The sympathetic portion of the molecule enhances the peripheral perineural vasoconstrictor response. The parasympathetic portion of the molecule may be concerned with the release of epinephrine from the adrenal gland. The sympathetic portion of the molecule is similar in structure to phenyl ethylamine while the parasympathetic portions are similar to acetylcholine. Apparently, both sympathetic and parasympathetic groupings are essential in the molecule but do not in themselves confer analgesic potency.

Nature of Receptors for Narcotics

The tertiary nitrogen atom is basic and yields a cation which is positively charged and becomes attached, by ionic bonding, to an anionic negatively charged site on the cell surface. In addition there appears to be an electrophilic *carbon group which is negatively charged* and which is attracted to a cationic positively charged site on the cell surface. This group bears an oxygen atom and is attached to the central carbon. The evidence at hand, then, indicates that the receptor sites on a cell surface are three in number (Fig. 1.18). These are (1) an anionic, negatively charged grouping in a concavity on the cell surface. The importance of this concavity is explained further on. (2) A cationic or positively charged site for the attachment of the electrophilic carbon grouping and (3) an intervening flat surface which extends between two electrically active sites and to which the cyclic portion of the molecule is attached.

Steric Configuration of Narcotics

It has been mentioned that the narcotic molecule is not planar, but instead has a three dimensional spatial configuration (Fig. 1.18). The morphine molecule is a complex composed of five rings, two of which are heterocyclic. One of these heterocyclic rings contains oxygen and one contains nitrogen. The nitrogen bearing ring is six-membered and is arranged in a planar fashion which is nearly perpendicular to the remainder of the molecule. This ring thus projects into space and, therefore, is believed to fit into some sort of a depression in the cell surface. The remainder of the molecule, that is, the bulky portion containing the phenyl and heterocyclic residues, is attached to the flat receptor area on the cell surface. The quaternary carbon forms the center of a nucleus of a large "umbrella-like" structure containing phenyl and heterocyclic residues. This portion of the molecule is attracted to the flat surface of the cell receptors area by forces of the Van der Waal type. Therefore, whatever bonding occurs from this attachment is weak. The firmness of the bonding of the molecule to the cell surface resides in the activity of the electrophilic groups. The marked differences in analgesic activity between optical isomers of various narcotics are explained by the proposal of a three dimensional arrangement of the molecule in space and that compounds whose projecting groups fit into the cavity show strong analgesic effects. Compounds having opposite steric configurations do not fit the cavity and, therefore, are inactive. As a rule only one of a pair of isomers is physiologically active. Levomorphan, for example, is active; while its dextro counterpart, dextromorphan, is devoid of narcotic action.
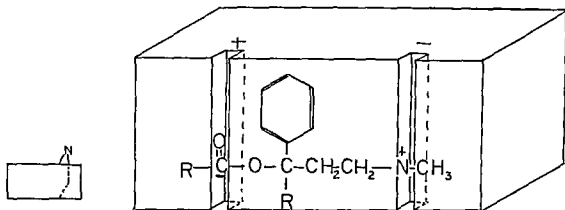
FIG. 1.18. Schematic representation of receptor for narcotic molecules. The negatively charged anionic site receives the positively charged nitrogen atom. The positively charged cationic site receives the oxygen carrying electrophilic carbon atom. The quaternary carbon atom bearing the benezine ring fits on to the flat surface of the receptor. The nitrogen portion of the molecule fits into a "depression" in the receptor since this portion projects into space at an angle from the flat portion of the molecule, making the structure three dimensional instead of planar. (See inset)

ELECTROPHILIC CARBON

The molecule must possess some degree of rigidity to maintain this necessary three dimensional configuration. This rigidity, as well as optical activity, is conferred by the quaternary carbon atom (Fig. 1.18).

The electrophilic carbon may carry a phenolic hydroxyl, as is the case in morphine and levallorphan, or it may carry a ketonic oxygen as is the case in methadon, meperidine and alphaprodine. Changes in the grouping attached to the electrophilic carbon lead to a reduction in activity. For example, methylation of the hydroxyl group in morphine results in codeine; in levorphan, levomethorphan. Both are weaker analgesics than the parent compounds from which they are derived. Meperidine and alphaprodine lose activity when the length of the carbon chain bearing the ketonic group is modified. Apparently these modifications of the electrophilic carbon alter the electronic attractive forces for the cationic center so that the strength of the bonding is weakened.

Replacement of the phenyl radicals in methadon, meperidine and alphaprodine by other groupings also leads to a decrease in activity. However, if the phenyl group in meperidine is replaced by a meta hydroxy group, phenyl keto bemidone results. This compound is markedly more active than meperidine (Table VI. 18).

EFFECTS OF ALTERING THE AMINO GROUP

Modifying the tertiary nitrogen atom on the methyl group also alters activity. Quaternization nullifies activity. Replacement of the methyl group of morphine by an allyl group, for example, results in nalorphine (Nalline). Replacement of the methyl group in levorphan by an allyl results in levallorphan (Lorfan). These act as narcotic antagonists when administered after morphine or other narcotics. Apparently they occupy the same site on the cell surface as the methyl nitrogen configuration. Nalorphine is weakly narcotic and analgesic. However, it displaces morphine and other analgesics from the site of

attachment on the receptor thereby substituting the weak analgesic effect of that possessed by nalorphine for the stronger one of morphine. The n-allyl structure presumably has a stronger power of attachment to the negative anionic site on the cell receptor than the n-methyl group of morphine and other narcotics. Apparently the double bond in the allyl group modifies the charge on the nitrogen atom to increase the strength of attraction for the anionic site. Both of the aforementioned allyl derivatives inhibit the narcotics by acting competitively with them. They are useful to overcome depression due to narcotics encountered clinically.

INDIVIDUAL NARCOTICS

The clinically useful narcotics appear to be predominantly in four series—the opiates which are predominantly derived from morphine, the morphinans which are synthetic phenanthrenes, the 4-piperidine types of which meperidine is the prototype, and the methadons which are diphenyl alkylamine derivatives. The individual members of these groups of clinical importance will be discussed in detail in the ensuing paragraphs.

MORPHINE

Structure

Morphine is the most important alkaloid in opium. The amount present ranges from 3% to 23% by weight but averages approximately 10%. Although opium has been known for centuries, the individual alkaloids contained in it were not identified until the turn of the 19th century. In 1805 Sertürner, a pharmacist, isolated morphine as a crystalline material from crude opium. This he called the "salt of opium." Even though the alkaloid was isolated more than one

hundred years ago, its structure was not accurately described until 1925. Until very recently, the exact molecular structure on the alkaloid was still uncertain until the compound was synthesized by Gates and Tschudi in 1952. The first structure was proposed by Knorr in 1882. Since then at least twenty other structures were proposed. The accepted structure is that proposed by Gulland and Robinson in 1925.

Reactivity

Morphine responds to certain tests characteristic of its side chains. The drug manifests properties characteristic of a tertiary amino group due to the presence of a nitrogen atom in one ring. The ethereal oxygen atom possesses the inertness characteristic of an ether. The phenolic hydroxyl responds to the tests of a phenol and the alcoholic hydroxyl to the usual tests and responses of a secondary alcohol. Two of the rings in the phenanthrene nucleus are partly hydrogenated.

The destructive distillation of morphine yields approximately 20% phenanthrene and other degradation products, such as ammonia, pyridine, and methyl amine. Acetyl chloride converts morphine to *diacetyl morphine* or *heroin*. Both hydroxyl groups are esterified by acylation. The substitution of the hydroxyls by other groups not only alters the intensity of the analgesic and narcotic properties, but also the central stimulating action. Chlorination with phosphorous trichloride attacks the alcoholic hydroxyl but leaves the phenolic group intact. The methoxy, as well as other alkoxy, groups may be made to replace one or both hydroxyls by treating morphine with a methylating agent. Codeine forms if only the phenolic hy-

droxyl is methylated, and thebaine if both are and the double bond in ring III is hydrogenated.

Formation of Salts

Morphine, by virtue of the phenolic hydroxyl, dissolves in strong alkalies to form salts. Thus, it is able to form a sodium salt. As is the case with other alkaloids, morphine is a base and forms salts with mineral and organic acids. In this case the salt formation is with the amino group. In the plant, morphine exists as a salt of naturally-occurring acids, such as meconic and lactic acid. The purified alkaloid is dispensed as a salt of a mineral acid usually as the hydrochloride or the sulphate.

Properties of the Base

The anhydrous free base is a white, odorless, bitter-tasting substance composed of fine, white rhomboid needles which melt at 254°C. and sublime at 200°C. The base is readily crystallized from amyl or methyl alcohols. A monohydrate crystallizes from water. Aqueous solutions are sufficiently alkaline to affect litmus as well as other indicators. The isoelectric point of morphine base, at which there is minimum solubility, is pH 8.96. The base is soluble in an excess of sodium or potassium hydroxide but not in ammonium hydroxide. The difference in solubility between weak and strong bases is utilized in extractions for toxicological studies.

The base is poorly soluble in water. One gram dissolves in 5000 cc. of water, 210 cc. of alcohol, 1220 cc. of chloroform, and 6250 cc. of ether at 25°C. The solubility in hot water is about five times greater than in cold. Morphine, like other alkaloids, possesses an asymmetric carbon and is optically active. The optical rotation of the base dissolved in 1% methyl alcohol is

$$[\alpha]_D^{25°} - 132°.$$

The naturally occurring optical isomer is levorotatory. The dextrorotatory derivative has been prepared synthetically.

Stability

Morphine is easily oxidized and converted, in alkaline solutions, to *pseudo-* or *oxydimorphine*. *Pseudomorphine* is a bimolecular structure made up of two rearranged molecules of morphine. Pseudomorphine is biologically inert and possesses no narcotic properties. It may form when morphine solutions stand in air or are boiled in the absence of acids, particularly in neutral or alkaline solutions. Permanganate solutions and other oxidizing agents hasten the conversion to the oxidation products. Morphine is also easily oxidized by salts of gold, silver, and platinum.

Morphine, boiled in aqueous alkali, is converted to methyl amine and other degradation products. Boiling with dilute acids causes the loss of one molecule of water and an internal rearrangement of the molecule. The resulting compound is *apomorphine*. The latter compound is a complex structure related to isoquinoline rather than phenanthrene.

Tests for Morphine

Morphine responds to several color reactions which may be used to identify the compound. A blue color forms with aqueous ferric chloride due to the presence of the phenolic group. Morphine may also be diazotized to produce a colored compound. This reaction, which is common to phenols and aromatic amines in general, may be used as a basis for a quantitative test for the alkaloid.

Frohde's reagent, added to morphine solutions, produces a deep purple color which is not obtained with codeine and atropine. A biological test is sometimes employed in which the test solution is injected into the back of a small white mouse. The animal assumes a position of lordosis, the tail becomes S-shaped, and the animal jumps at the slightest stimulus if morphine is present.

Properties of Salts

The commonly employed salts are the *sulphate* and the *hydrochloride*. Salts are more soluble in water than the free base. The *sulphate* is a white powder which melts with decomposition at 250°C. One gram dissolves in 15.5 cc. of water at 250°C. It is slightly soluble in alcohol, but insoluble in ether and chloroform. Aqueous solutions of morphine sulphate are acid to litmus (pH 4.8). The sulphate is also levorotatory

$$[\alpha]_D^{25°} -94.5°$$

in a 4% aqueous solution. Morphine sulphate possesses five molecules of water of crystallization, as shown by the empirical formula, $(C_{17}H_{19}O_3N)_2 \cdot H_2SO_4 \cdot 5H_2O$. Three are lost at 100° and the remainder at 130°C. The *hydrochloride* possesses three molecules of water of crystallization which are lost at 100°C. The hydrochloride is soluble in water (1 gm. in 17.5 cc.), alcohol and glycerine, but insoluble in chloroform and ether. The pH of dilute aqueous solutions of the hydrochloride is 5.0. Other salts of morphine are the acetate, bimeconate, citrate, hydroiodide, hydrobromide, lactate, meconate, nitrate, oleate, phosphate, phthalate, sterate, tartrate, and valerate. The nitrogen atom, since it is a tertiary amine, adds methyl bromide to form the pentavalent nitrogen com-

pound, morphine methyl bromide. Quaternization of the nitrogen decreases activity. A 3% solution of morphine sulphate, referred to a Magendie's solution, was once extensively used for parenteral or subcutaneous administration. Solutions are best stored in amber or dark bottles to prevent decomposition.

Distribution in Tissues

Morphine is absorbed readily after parenteral injection. The drug penetrates the mucous membranes. Absorption from the stomach is variable, depending upon the pH of gastric contents. The distribution of morphine is uniform in most tissues. The drug does not appear to concentrate in the brain even though its principal site of action is there. Morphine exists in free and bound form after parenteral administration. Peak levels can be correlated with pharmacological activity. Morphine traverses the placental barrier.

Excretion

Morphine is excreted into the gastrointestinal tract and in the urine. Oberst found that the morphine excreted in urine exists in two forms—free and bound. Over 90% of a dose of morphine may appear in the excreta. The fate of the remainder is unknown. The greater portion of a dose undergoes conjugation chiefly by the liver. The conjugated product is excreted into the urine by the kidney. The ratio of unbound morphine is increased in the presence of liver damage. The most rapid excretion occurs within the first two hours. The major portion is eliminated within twenty-four hours. However, traces may be detected in the urine for several days. Seven to ten per cent of a dose in man is recoverable in the urine. The intestinal morphine reaches the tract via the bile into which it is

excreted. The bound morphine of the bile is morphine glycuronide dihydrate. The bound urinary morphine is a monoglucuronide. The union with glucuronic acid is by a glucoside linkage by the aldehyde group of the acid to either the phenolic or alicyclic hydroxyl group. A di-conjugated compound is also present in which a glucuronic group attaches to the alicyclic hydroxl and an ethereal sulphate to the phenol. The conjugates are physiologically inert. The conjugation is aided by microsomal enzymes in the hepatic cells. The bound form may be hydrolyzed to morphine after prolonged boiling in acid solution. The amount of free morphine in urine of addicts is 4% to 5% of the daily intake.

Morphine is stored presumably in muscles, but the storage capacity is probably limited since the amount excreted in addicts falls to a low level the first and succeeding days of abstinence. After five days, practically no morphine is found in the urine of these subjects. Less morphine is excreted when administered orally than subcutaneously. This difference is probably due to possible destruction by the liver or to loss in the gastrointestinal tract.

Morphine sulphate is the salt of the alkaloid which is official in the U.S.P.

Codeine

Source

Codeine is also derived from phenanthrene. The alkaloid occurs in opium in quantities varying from 0.2% up to 0.8%, usually averaging 0.5%. Chemically, codeine is methyl morphine. The methyl ether group replaces the phenolic hydroxyl. The phenolic hydroxyl of morphine is more readily etherified than the alicyclic hydroxyl, although it is possible to etherify both to form dimethyl morphine. Codeine was first isolated from opium by Robiquet in 1832. The alkaloid is found in no other plant but the poppy and it is believed to form after morphine.

Synthesis from Morphine

The greater part of commercial codeine is obtained by methylation of morphine which is a more abundant product. Methylation may be accomplished on a commercial scale by allowing morphine to react with methyl sulphate, $(CH_3)_2\cdot SO_4$, or trimethyl ammonium hydroxide, $-(CH_3)_3 \cdot NH \cdot OH$.

The latter reagent is preferable as the loss of morphine is least and the yield of codeine is highest due to minimal side reactions. A by-product, dimethyl analine forms which is removed by distillation.

Solubility

Codeine crystallizes from ether or benzine in small, anhydrous prisms. The free base melts at 154° to 156°C. It is sparingly soluble in water (1 part in 120), but soluble in organic solvents such as alcohol (1 gm. in 2 cc.), chloroform (1 gm. in 0.5 cc.), and ether (1 gm. in 18 cc.) and benzine (1 gm. in 13cc.), at 25°C. Codeine is levorotatory,

$$[\alpha]_D^{25°} = -134°.$$

Aqueous solutions of the base turn red litmus blue. The base forms a hydate with a single molecule of water. A variety of salts is prepared among which are the acetate, citrate, hydrobromide, nitrate, and salicylate. The *hydrochloride, sulphate,* and *phosphate* are the most commonly employed salts. The base, the phosphate and sulphate are official and included in the U.S.P. The phosphate forms a hydrate with 1½ molecules of water ($C_{18}H_{21}O_3N\cdot H_3PO_4\cdot 1\frac{1}{2}H_2O$). The sulphate forms a hydrate with 5

molecules of water ($C_{18}H_{21}O_3N \cdot H_2SO_4 \cdot 5H_2O$). The phosphate is the most soluble salt of codeine and is, therefore, popular for parenteral use. One gram dissolves in 2.3 cc. of water at 23°C. One gram of the sulphate dissolves in 30 ml. of water in similar circumstances. The salts are poorly soluble in alcohol, chloroform and ether.

Stability

Codeine resists oxidation more than morphine due to muzzling of the phenolic hydroxyl group. Oxidation with permanganates or chromic acid converts the alicyclic hydroxyl to a ketone group and forms *codeinone*. Codeine possesses the properties of a secondary alcohol, but none of a phenol, since the phenolic hydroxyl is masked by the methyl radical.

Concentrated sulphuric acid or anhydrous oxalic acid cause the loss of a molecule of water and convert the alkaloid to *apocodeine*. This compound bears the same relationship to codeine that apomorphine has to morphine.

Codeine, as does morphine, forms precipitates with alkaloidal reagents. Ferric chloride produces no purple coloration due to absence of the phenolic hydroxyl group. A drop of a mixture of sulphuric and nitric acids added to codeine produces a green color which ultimately turns violet green. Codeine warmed with a few drops of nitric acid, followed by a drop of alcoholic potassium hydroxide, turns brick red. A white precipitate forms when a few drops of phosphotungstic acid reagent is added to an aqueous solution of codeine. Dry codeine mixed with several times its bulk of potassium arsenate produces a deep blue color when a drop of concentrated sulphuric acid is added.

Absorption and Elimination

The absorption and distribution of codeine parallels that of morphine. Absorption proceeds at a somewhat more rapid rate than that of morphine by either the parenteral or oral route. The bulk of a given therapeutic dose of codeine is excreted in a bound form. A portion of it is demethylated by removal of the methyl group on the nitrogen atom and excreted as *norcodeine*. This in turn is bound with glucuronic acid and excreted. A trace is converted to morphine and this in turn is conjugated and excreted in the bound form. Only traces of unbound norcodeine and morphine appear in the urine. The intestinal excretion is negligible.

Ethyl Morphine (Dionine)

Ethyl morhpine or *dionine* is a synthetic substance prepared from morphine. An exothy group instead of a methoxy masks the phenolic hydroxyl of morphine (Table II.18). The base forms salts the most important of which is the hydrochloride. This forms a hydrate with two molecules of water. This salt is in most respects similar to codeine.

Pharmacologically and chemically dionin is similar to codeine. Like many narcotics it manifests local anesthetic activity. The fate in the body has not been determined.

Dihydromorphine (Paramorphan)

The double bond of morphine between carbon 7 and 8 may be hydrogenated to form dihydromorphine, which is somewhat similar to morphine in properties and activity but less potent. It is prepared by reducing morphine with hydrogen in the presence of palladium as a catalyst. The base reacts with acids to form salts the most important of which is the hydrochloride. The base is insolu-

ble in water, but soluble in organic solvents. The salt is water soluble. Similar hydrogenation of codeine results in dihydrocodeine. The base forms a dihydrate which is a white powder melting at 187–189°C. The pharmacologic behavior and potency are similar to codeine.

DIACETYL MORPHINE (HEROIN)

Diacetyl morphine is made by esterifying morphine with acetic acid. Both hydroxyl groups are esterified. Diacetyl morphine is a white, odorless, bitter crystalline powder which melts at 172°C. One gram dissolves in 1700 ml. water, 31 ml. alcohol, 1.5 ml. chloroform and 100 ml. ether. The hydrochloride is a white, odorless, crystalline powder which melts at 230°C. The salt is levorotatory

$$[\alpha]_D^{26°C} - 153°$$

in water. The hydrochloride is soluble (1 part in 2 of water), moderately soluble in alcohol but insoluble in chloroform and ether.

Diacetyl morphine is rapidly absorbed from mucous surfaces and subcutaneous and intramuscular tissues. The distribution in the body is similar to that of morphine. Diacetyl morphine is hydrolyzed to morphine in the body. The morphine is then excreted in a conjugated form in the urine. Approximately 7% is eliminated as free morphine. The compound is hydrolyzed in the body and is excreted as morphine in a bound form.

DIHYDROMORPHINONE (DILAUDID)

Structure

Dihydromorphinone (Dilaudid) is a synthetic narcotic derived from morphine. As is the case with morphine, three oxygen atoms are also present in dihydromorphinone. The phenolic hydroxyl in position 3 and the ethereal oxy-

gen are unaltered but the alicyclic hydroxyl (position 6) (secondary alcohol) is converted into a ketonic oxygen group. The narcotic potency of the drug is enhanced 8–9 times by the changes. Pharmacologically the drug is qualitatively similar but quantitatively different from morphine.

Dihydromorphinone is prepared by hydrogenation of morphine in an acid solution in the presence of a catalyst, such as platinum. The double bond ordinarily present between carbons 7 and 8 (Table II.18) in the morphine structure is removed. The hydroxyl group is converted to a ketone by oxidation.

Properties

Dihydromorphinone is a fine, white, odorless powder, soluble in water (1 to 3 at 20°C.) and in alcohol, but insoluble in ether. The free base forms salts with mineral acids. The hydrochloride is the most common and important salt. The base, like that of morphine, decomposes when heated (M.P. 260° to 262°C.). Aqueous solutions of the hydrochloride may be sterilized by boiling. The compound is levorotatory.

Reactivity

Both the phenolic hydroxyl and the ketonic group are reactive and respond to tests and reactions characteristic of phenols and ketones. Dihydromorphinone manifests the same behavior as do other ketones and forms an oxime when treated with hydroxylamine hydrochloride. One part of hydroxylamine and five parts of Dilaudid react to form a precipitate after alkalinization with ammonia. The oxime may be used for identification since the precipitate melts at 230°C. to 235°C. A blue color results when ferric chloride is added to aqueous solutions of

dihydromorphinone due to the presence of the phenolic hydroxyl in position 3. This color, which is also obtained with morphine, is absent in acid solutions and in ether.

DIHYDROCODEINONE

Dihydrocodeinone (Dicodid, Hycodan) bears the same relationship to codeine that dihydromorphinone bears to morphine. Hydrogenation of the double bond between carbon 7 and 8 and conversion of the alicyclic hydroxyl group of codeine to ketone forms dihydromethyl morphinone (Table II.18). A hydroxyl group in position 14 results in dihydrohydroxy codeinone (Eucodal). An enol acetate may be formed by refluxing dihydrocodeinone with acetic anhydride and sodium acetate. The linkage of the acetate is at position 6. This compound, known as *acedicon*, is somewhat more potent than dihydrocodeine.

METOPON (METHYL DIHYDROMORPHINONE)

Metapon is similar in structure to dihydromorphinone save for the presence of a methyl group instead of a hydrogen atom in the 7 position. It is prepared from thebaine. The drug is less addicting than morphine but more analgesic.

OXYMORPHONE

Another derivative closely allied to dihydromorphinone recently introduced is 14 hydroxy dihydromorphinone (Numorphan). This resembles morphine and dihydromorphinone in pharmacologic properties.

APOMORPHINE

Formation

Apomorphine is little used in anesthesia practice but is mentioned because of its close relationship to morphine and interest in its emetic qualities. The drug is a synthetic base which is formed from morphine by internal rearrangement of the molecule. This comes about by treating the morphine with sulphuric acid at 40°C. A molecule of water is lost, the bridge containing the nitrogen is altered, and the inert ether linkage of morphine is converted into a second, phenolic hydroxyl group. The structure may be considered a derivative of phenanthrene and isoquinoline (Table III.18). These changes produce a marked diminution of the narcotic effect but an enhancement of stimulating effects. Apomorphine is usually employed as an emetic.

Properties

Apomorphine is a white or grey-white powder which acquires a greenish tint when exposed to air. The presence of the two phenolic hydroxyls on the molecule renders the compound unstable in air. Like other phenols, it is oxidized to quinones and absorbs oxygen quantitatively in the change. A green coloration indicates that the solution has deteriorated. The *hydrochloride* and the *sulphate* are the most common salts. The hydrochloride forms a hemihydrate which is soluble in water (1 in 50). Apomorphine responds to the reactions and tests of phenols and ketones which may be used for identification. Apomorphine hydrochloride is included in the U.S.P.

PAPAVERINE

Papaverine is the most important of the opium alkaloids derived from isoquinoline. It occurs in opium to the extent of 1%. It is also prepared synthetically. Structurally papaverine is a tetra-methoxy-benzyl-isoquinoline.

The alkaloid possesses an anti-spas-

modic as well as an analgesic action. It is non-narcotic and is devoid of central action.

Papaverine was discovered in 1848 by H. Merck. The alkaloid is a feebly basic substance which is optically inactive. It occurs as a white powder which melts at 147°–148°C. Papaverine base is insoluble in water but soluble in alcohol (1 part in 45 at 25°C.) The hydrochloride is the most common salt, although the nitrate and sulphate are also prepared. The hydrochloride is soluble in water (1 to 40) and alcohol and chloroform but insoluble in ether. Aqueous solutions are acid in reaction.

Absorption and Fate

Papaverine is absorbed from the mucous membranes and from subcutaneous and intramuscular tissues after injection. It is not recoverable in the urine or feces. It is believed to be acted upon by the microsomal enzyme system in the liver. Formaldehyde and a phenolic metabolite result.

MORPHINAN SERIES

The closest synthetic approach to the morphine structure has been the synthesis of morphinan derivatives. The skeleton of morphine minus the alicyclic hydroxyl, the ether bridge and the double bond in the 7–8 position forms the basis of this series of compounds (Table IV.18). The heterocyclic ring (V) containing the nitrogen atom is arranged in the same manner and is in the same position as in morphine. The compound carries the phenolic hydroxyl. The cyclic oxygen ring found in morphine (V) apparently is not necessary for narcotic activity, since levorphanol is 5 times more potent an analgesic than morphine. The methyl group on the nitrogen atom ap-

parently is essential since an ethyl or allyl group nullifies narcotic potency. A number of morphinan derivatives have been prepared among which the most prominent are N-methyl morphinan, 3 hydroxy N-methyl morphinan, 2 hydroxy N-methyl morphinan and 3 hydroxy N-benzyl morphinan.

LEVORPHANOL AND RACEMORPHAN (DROMORAN)

The most important of the morphinan series is 3 hydroxy N-methyl morphinan. This structure has three asymmetric carbon atoms. The racemic mixture is known as racemorphan (Dromoran). Racemorphan may be separated into its isomers by means of differential solubilities of its tartrates. The levo isomer, known as *levorphanol*, is the active component. The d,l mixture was originally used therapeutically. The levorphanol possesses twice the analgesic activity of the racemic form. The dextro isomer not only has no analgesic activity but is even believed to antagonize the respiratory depression and analgesic effect of the levorphanol. The dextro derivative is said to possess antitussive activity.

Levorphanol is promptly absorbed when administered orally or after subcutaneous injection. Maximum analgesia occurs within 60–90 minutes. About 2 to 7% of the dose is excreted into the urine unchanged. Twenty to 40% is conjugated, presumably with glucuronic acid, after which the conjugate passes into the urine. The mechanism of detoxification varies from species to species.

Levorphanol is prepared as the tartrate which is a white, odorless, crystalline powder. The compound is stable to light, heat, air and moisture. Solutions are slightly acidic having a pH range of 3.4–4.0. It is slightly soluble in alcohol

and sparingly soluble in water. The drug was introduced in 1953. The compound responds to the tests for phenols since the hydroxyl group on position 3 is phenolic.

METHOXYMORPHINAN

The hydroxyl group in position 3 may be methylated to form methyl ethers (Table IV.18). These methyl ethers have the same relationship to levorphanol that codeine has to morphine. The racemic methomorphinan is a mixture of the dextro and levo isomers. The levo isomer is the active component. This derivative is narcotic and resembles codeine in its pharmacologic behavior. The dextro component is inactive. It does, however, manifest anti-tussive properties and is used for this purpose (Romilar). The racemic mixture is half *as potent as the* levo derivative.

Dextromethomorphinan (Romilar) is prepared in the form of the hydrobromide. It is freely soluble in alcohol, but sparingly soluble in water.

LEVALLORPHAN

Replacement of the methyl group on the nitrogen atom of levorphanol by an allyl group results in a compound which is almost devoid of narcotic activity but appears to have considerable reactivity for the receptors for the narcotic in the medullary centers. This N-allyl derivative is known generally as levallorphan (Lorfan). Levallorphan is capable of displacing *more potent narcotics, such as* morphine, levorphanol from the respiratory centers and thus acts as an antagonist (Chap. 24).

BENZMORPHAN SERIES

PHENAZOCINE

Further modification of the phenanthrene ring may lead to synthesis of a series of derivatives known as the benzmorphans of which the most important is phenazocine. In the benzmorphan nucleus ring III of the morphinans and morphinoids has been eliminated (Table V.18). A methyl group remains as a residue of this ring to maintain the quaternary carbon atom which is essential for narcotic activity. Ring V is formed and attached in the same way as it is in morphine. The nitrogen atom on the dimethylene containing ring is the same as in morphine. The 2-hydroxy-2-5 dimethyl 6, 7 benzmorphan is only one-fifth as potent as morphine. A methyl group in position 9 of ring II gives a structure which approximates that of methyl morphinan. By altering the substituent on the nitrogen atom so that a phenyl ethyl group replaces the methyl, the potency is *increased to ten times that of morphine*. This derivative is phenazocine (Prinadol, NIH 7519). Actually this compound is morphine minus ring III which is replaced by a methyl group, minus the ether linkage and the alicyclic hydroxyl.

PIPERIDINE SERIES

MEPERIDINE (DEMEROL)

Structure

A number of synthetic narcotics are derived from N-methyl piperidine. The first to be prepared, the most widely and best known in this group is meperidine (Demerol) (Table VI.18). Eisleb and Schaumann described its synthesis and pharmacological properties in 1939. These workers were in search of a compound with anticholinergic properties which would block the action of acetyl choline, as does atrophine. The drug is also known as pethidine, dolantin, eudolat and isonipecaine.

Meperidine is derived from a hydrogenated pyridine structure. The nitrogen

TABLE VI.18
PIPERIDINE SERIES

Piperidine

Meperidine

Nor-Meperidine

Bemidone

Ketobemidone

Anileridine
(Leritine)

Alphaprodine
(Nisentil)

Ethoheptazine
(Zactirin)
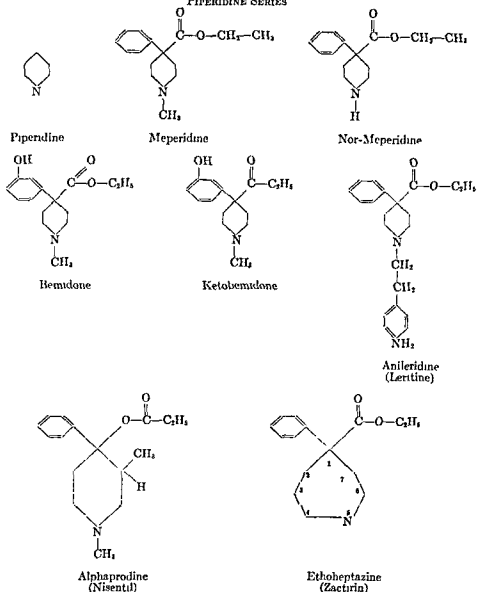
atom is in the ring. A methyl group is present on the nitrogen atom as it is on the majority of the narcotics. A phenyl group is present on the carbon in position 4. In addition carbon 4 carries a carboxylic group which is esterified with ethyl alcohol. Carbon 4, therefore, is the quaternary carbon so essential for narcotic action. The carbonyl group of the carboxyl radical is the electrophilic carbon atom. The nitrogen atom in piperi-

dine is separated from the quaternary carbon in position 4 by two carbon atoms. The structure of meperidine therefore conforms to the configuration alleged to be essential for narcotic activity. The structure of meperidine may be written in a variety of ways so that it can be made to bear some resemblance to morphine, to atropine and to the general configuration characteristic of local anesthetics.

Meperidine exhibits a narcotic action with a marked analgesic component and a mild sedative effect, a spasmolytic effect on smooth muscle like papaverine, a feeble local anesthetic action like cocaine, and anticholinergic action like atropine. The resemblance of meperidine to morphine is strongest when the nitrogen-containing heterocyclic ring in morphine is written to have a piperidine-like configuration. Cocaine and atropine both have similar cyclic structures. They both have a five-membered ring fused with a six-membered ring in which the nitrogen atom is common to both rings. The six-membered ring is a piperidine ring.

Properties

Meperidine is a stable, white, crystalline powder. It is odorless, readily soluble in water and aqueous acid solutions. The drug forms salts with acids and is dispensed as the hydrochloride. The salt is stable at room temperature. Aqueous solutions have a pH of 6 and do not decompose on boiling.

Distribution and Metabolism

Meperidine is readily absorbed from the intestinal tract and from subcutaneous and intramuscular tissues. Approximately 5% of a therapeutic dose is excreted unchanged in the urine, 5% in the form of normeperidine (demethylated at the nitrogen atom), 12% as the de-esterified acid and 12% as the de-esterified normeperidine. The liver plays the dominant role in the inactivation. Duration of hypnosis is prolonged in hepatectomized animals. The enzyme responsible for the hydrolysis is distinct from the cholinesterases, the tropine esterases and the aliphatic esterases. Tolerance does not alter the role of metabolic alteration.

Distribution studies in animals reveal no extensive localization in any tissues. Accumulation does not occur in the body. Ten hours after administration none is detectable in the plasma. The decline in plasma levels averages 17% per hour after an intravenous injection. The method and rate of meperidine detoxification varies with the species.

A number of closely allied derivatives are made by altering the meperidine structure. Introduction of a hydroxyl, methoxy or amino group into the phenyl radical attached on the 4 position of the piperidine ring diminishes potency. One compound (bemidone), however, in which there is substitution of a hydroxyl group in the 3 position of the phenyl group is equal in potency to meperidine. The ethyl ester is the most effective compound. Esterification with alcohols of higher molecular weight other than ethyl diminishes potency. Substitution of groups other than methyl on the piperidine ring diminishes potency, unless it is an ethyl-phenyl, which seems to increase potency. The phenyl radical on carbon 4 is essential for narcotic activity. Replacement of the phenyl group by benzyl or naphthyl groups diminishes potency. The presence of the acyloxy radical,

$$(-O-\overset{\overset{\displaystyle O}{\|}}{C}-R)$$

on carbon 4 is essential. Shifting the phenyl and the acyloxy groups from position 4 to another position on the piperidine ring, for example, to position 2, nullifies narcotic activity. The presence of a carbon to carbon union between carbon 4 and the acyloxy group results in less potent compounds than a carbon to oxygen linkage. Thus, alphaprodine (Nisentil) which has an oxygen to carbon linkage,
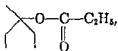
is more potent than meperidine which has a carbon-carbon linkage on carbon 4,
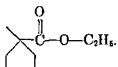
Replacement of the ester side chain by a ketone group increases potency. Replacement of the ester side chain in bemidone results in ketobemidone which is twenty times more potent than bemidone or meperidine, but far more addicting.

Enlarging the ring in meperidine so that it has seven instead of six members, results in a derivative known as azocycloheptane. Such a seven membered ring carrying the same substituents on the ring as meperidine (Zacterin) has some analgesic potency but less than that of codeine. The compound is non-addicting, non-hypnotic and does not cause euphoria. It has a central carbon atom, the amino nitrogen and the methylene chain connecting the active components.

Alphaprodine (Nisentil) is the reversed ester of meperidine. In other words, the hydroxyl group which takes part in the esterification is on the 4 position of piperidine instead of the ethyl group. The piperidine nucleus acts as the alcohol which is then esterified with propionic acid. Thus, the 4 carbon is attached to the ester linkage by an oxygen atom instead of by a carbon atom as in meperidine. In addition a methyl group is present on position 3 of the piperidine nucleus (Table VI.15). The compound is racemic so that a beta form is also avail-

able. The beta form may be resolved by means of tartrates into the levo and dextro components. The compound is several times more potent than meperidine but shorter lasting. It is less effective orally than parenterally.

ANILERIDINE (LERITINE)

It has been generally accepted that the methyl group on the nitrogen atom confers optimal activity on all potent narcotics. It has since been shown that substitution of a phenyl ethyl group for a methyl group confers increased activity to certain compounds (Table V.18). This led to the synthesis of a compound known by the generic name of Anileridine. Structurally it is similar to meperidine with the exception that the methyl group is replaced by a phenyl ethyl group (Table V.15). An amino group appears on the 4 position of the phenyl in this side chain. The analgesic potency is approximately two and a half times that of meperidine and approximately one fourth of morphine.

METHADONE SERIES

METHADONE

During World War II methadone, a member of a series of compounds numbered I.G. 10820 of the I. G. Farben industrie of Germany, was used extensively as an analgesic. This compound is an aromatic and amino substituted heptanone. At first glance its structure appears to be unrelated to the morphinoids and compounds in the piperidine series. Closer examination of its structure reveals, however, that the groupings essential for narcotic activity are present in this compound also (Table VII.18). Carbon 4 in the heptane chain carries two phenyl groups; carbon 3 a ketonic oxy-

TABLE VII.18
METHADONE SERIES
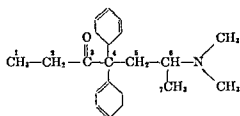
Methadone
d, l, or dl, dimethyl amino
diphenyl heptanone
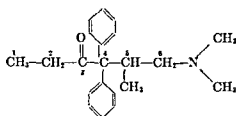
Isomethadone
d, l, or dl, dimethyl amino
diphenyl methyl hexanone
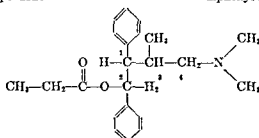
Propoxyphene (Darvon), dimethylamino
amino methyl butanol propionate

gen atom and carbon 6 an amino nitrogen which has two methyl groups. Carbon 4, the quaternary carbon, is separated from the amino nitrogen by the dimethylene chain (—CH₂—CH₂—) which is deemed essential for narcotic activity. It also carries two phenyl groups which give the essential bulkiness to the molecule. These are attached to the ketonic bearing electrophilic carbon atom. Carbon 4 is asymmetric; therefore, the compound is optically active. The levo isomers are active derivatives; the dextro are not. The analgesic potency of methadone approximates that of morphine. Methadone is a base which forms a hydrochloride which consists of a powder composed of colorless, white crystals. It is very soluble in water. Solutions have a pH of 6.0. The compound is stable in air. Methadone is metabolized in the body presumably by the liver. Six to 12% of single doses administered subcutaneously in humans are excreted into

the urine. Some is excreted into the bile and hence into the bowel.

METHADOLS

Reduction of the ketonic group with hydrogen converts the compound to an alcohol known as *methadol*. The alcohol is less potent than the ketone. The alcohol may be separated into an alpha and a beta component and each of these has a dextro and levo isomer. Acetylation of the alcohols forms *acetmethadol*. This is more potent than methadol and other substituents, but appears to be more toxic than methadon.

ISOMETHADONES

A series known as the isomethadones differs from the methadones in the placement of a methyl group closer to carbon 4. Levo and dextro isomers are known. The isomethadones are analgesic, less toxic and less addicting than the normal derivatives.

DEXTROPROPOXYPHENE (DARVON)

Dextropropoxyphene is a base which possesses analgesic potency similar to codeine. The compound is a tertiary amino ester of propionic acid. It bears no resemblance to the morphinoids, morphinans, benzmorphans or piperidine type compounds. Although not related to the methadones, it resembles these more than any other groups mentioned in the previous discussion. Chemically it is dimethyl amino 1, 2, diphenyl 3, methyl-2-butanol propionate. Its structure fulfills the requirements of a narcotic having an amino group on a dimethylene chain attached to a quaternary carbon, with a phenyl group and an electrophilic carbon. The compound is believed to be non-addicting but does relieve to a limited extent the symptoms of withdrawal in narcotic addicts. The toxicity is low. Its fate in the body is unknown. It is absorbed from the gastrointestinal tract.

Amides, Ureides, and Barbiturates

NITROGEN CONTAINING COMPOUNDS

THE NON-VOLATILE central nervous system depressants described thus far have been aliphatic compounds, chiefly alcohols or esters. Nitrogen and cyclic structures have not appeared in the molecular structures. The compounds to be discussed presently are nitrogen containing substances. Some are heterocyclic structures. Nitrogen containing central nervous system depressants are either amines or amides. The amino group is of less importance in the hypnotics and prominent in the narcotics. The non-narcotic depressants are amides, derivatives of amides or heterocyclic nitrogen containing structures. This chapter will deal principally with amides or their derivatives, the most important of which are the carbamates and the ureides.

AMIDES

Amides are formed when the hydroxyl portion of a carboxyl group of an *organic* acid is replaced by an amino group:

$$-\underset{\underset{O}{\|}}{C}-OH \qquad -\underset{\underset{O}{\|}}{C}-NH_2$$

Amides possess no hypnotic activity unless one or more hydrogen atoms of the amino group are replaced by alkyl, aryl, or acyl radicals to form substituted amides. Acids with two carboxyl groups may have each hydroxyl of the carboxyl group replaced by amino groups to form *diamides.* Substituted amides of both monocarboxylic and dicarboxylic acids have been prepared but are unimportant clinically and, therefore, will be passed over in this discussion. Carbonic acid, though not a carboxylic acid, behaves like one. It acts like a dicarboxylic acid and yields two hydrogen ions. It, therefore, forms both a monoamide and a diamide. The structure of carbonic acid is often represented graphically as follows:

$$\underset{OH}{\overset{OH}{\diagup}}C{=}O$$

One hydroxyl group may be replaced by an amino group to form the monoamide,

$$\underset{OH}{\overset{NH_2}{\diagup}}C{=}O$$

or *carbamic acid.* When both hydroxyls are substituted, the diamide,

$$\underset{NH_2}{\overset{NH_2}{\diagup}}C{=}O$$

or *urea* results. The hydrogen of the hydroxyl group of carbamic acid ionizes to form hydrogen ions. Carbamic acid is esterified with various aliphatic and cyclic alcohols to form important central nervous system depressant drugs. The diamide, of carbonic acid is urea.

Urea, forms the basis of a variety of soporific, hypnotic, or anesthetic substances. Urea by itself is non-hypnotic. Its chief use is as a diuretic and dehydrating agent. The hydrogen atoms of the amino group of urea are replaced by radicals to form substituted ureas. Urea reacts with acids to form a class of compounds known as ureides of which the barbiturates, the hydantoins and the purines are important members.

CARBAMATES (URETHANES)

When carbamic acid is esterified with monohydric aliphatic alcohols a group of compounds known as *urethanes* results. The ester prepared from ethyl alcohol,

$$C_2H_5-O-\overset{\displaystyle O}{\underset{\displaystyle \|}{C}}-NH_2$$
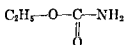
known as ethyl urethane, is the simplest, most important member of this series of compounds. It is little used as a hypnotic in man because it is a comparatively weak hypnotic. It has been used to suppress bone marrow activity. The potency of urethanes increases as the molecular weight of the alcohol used in the esterification increases. The potency, likewise, varies with the type of alcohol used to form the ester. Esters prepared from secondary alcohols are more potent than those formed from primary, while esters formed from tertiary alcohols are more potent than those formed from secondary. *Hedonal*, a urethane formed from methyl propylcarbinol, a secondary alcohol, was once a popular hypnotic. It has the following structure:

$$C_3H_7-\overset{\displaystyle H}{\underset{\displaystyle CH_3}{C}}-O-\overset{\displaystyle O}{\underset{\displaystyle \|}{C}}-NH_2$$
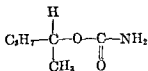
Aponal, the ester of tertiary amyl alcohol

(amylene hydrate) is more potent and is more effective clinically than hedonal, its isomer:

$$C_2H_5-\overset{\displaystyle CH_3}{\underset{\displaystyle CH_3}{C}}-O-\overset{\displaystyle O}{\underset{\displaystyle \|}{C}}-NH_2$$
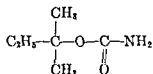
Halogenated alcohols also form esters. Aleudrin, the carbamic acid ester of dichloroisopropanol and Voluntal, the ester of trichlorethanol are more toxic and more depressant than urethane. The urethanes have gone unnoticed for many years. However, recently there has been a revival of interest in these substances and series of higher molecular weight compounds have been prepared. Ethinamate (Valmid) is one of these. Structurally it is cyclo hexenyl carbamate. Esters of dihydric alcohols derived from propane have a tranquilizing effect. Instead of exerting their primary effect on the cortex they depress the hypothalmic region. Among these are meprobamate (Equanil, Miltown) and the dicarbamate ester of mephanesin.

The exact fate of most urethanes has not been established. Approximately 20% of a therapeutic dose of urethane is metabolized. The remainder is excreted unchanged. The metabolized fraction is probably inactivated in the body by hydrolysis to alcohol and carbamic acid. Carbamic acid is probably converted to and eliminated as urea. It is surmised the other urethanes are hydrolyzed. The alcohols are either eliminated unchanged by the lungs or the kidneys, or are conjugated or oxidized to carbon dioxide and water by some biochemical mechanism.

SUBSTITUTED UREAS

Urea is a white powder which is very soluble in water. Aqueous solutions are

feebly basic. Urea forms salts with mineral and organic acids. Heat, bacterial fermentation, and enzymic hydrolysis convert urea to ammonia and organic carbonates. One or both hydrogen atoms of each amino group may be substituted by alkyl, aryl, acyl, or other radicals to form substituted ureas. These, as has been stated previously, possess hypnotic properties. However, they are of low potency or toxic and are, therefore, seldom used. Hypnotic properties are more apparent when the substituting groups are alkyl groups. Substitution of alkyl radicals derived from secondary alcohols results in compounds of greater potency than those having radicals derived from primary alcohols. Radicals derived from tertiary alcohols confer greater potency than those derived from secondary. Hjort and co-workers compared the hypnotic potencies of a homologous series of substituted ureas and found that the potencies increased approximately twofold for each addition of a CH_2 group in the aliphatic radical. Molecular weight is the determining factor in hypnotic effectiveness. Alkyl group substitution results in compounds which are effective, while the use of aryl groups does not. The substitutions may be unsymmetrical (that is, on one amino group), or symmetrical (one substituent on each group). The *isoalkyl* ureas are less active physiologically than normal alkyl isomers. In a homologous series, the lethal and hypnotic doses vary directly with the water solubility and distribution coefficients of each member. The introduction of a carboxyl or hydroxyl group as the substituting group decreases the potency, while halogenation, as is the case with other hypnotic drugs, increases the potency.

Acyl-substituted ureas have been used clinically. *Sedormid,* or allyl-isopropyl acetyl-urea was once employed as a sedative, but was found to suppress bone marrow activity.

Carbromal, or bromodiethylacetyl-urea was once included in the U.S.P.

Bromural, likewise, was official. It is also an acyl derivative of a complex aliphatic acid. Substituted ureas as a general group are not effective as hypnotics and are of little clinical importance.

UREIDES

Urea interacts with aliphatic carboxylic acids to form compounds known as *ureides.* One hydrogen of an amino group combines with the hydroxyl of the carboxyl to form an imide linkage

$$-\overset{|}{N}-H$$

and a molecule of water. Acids having two carboxyl groups form cyclic ureides. *Both amino groups of the urea and each hydroxyl of both carboxyl groups of a dicarboxylic acid interact to form cyclic ureides.* When malonic acid and urea interact malonyl urea or barbituric acid is formed:
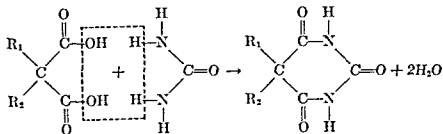
HYDANTOINS

Glycollylurea, or *hydantoin*, results from condensation of urea and glycollic acid. The resulting five-membered ring structure is the basis of several important sedative and anti-convulsant drugs.

$$
\begin{array}{c}
\text{O} \\
\| \\
\text{C}_1\text{—N—H} \\
| \qquad | \\
\text{C}=\text{O} \\
| \qquad | \\
\text{H—C}^5\text{—N} \\
| \\
\text{H}
\end{array}
$$
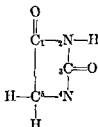
If the two hydrogen atoms attached to the carbon in position 5 are replaced by a phenyl and an ethyl group, respectively, phenylethyl-hydantoin, or *nirvanol*, forms. If two phenyl groups are substituted, diphenyl-hydantoin, or *dilantin*, forms. Both are drugs which depress the central nervous system and act on the motor cells of the cortex.

Oxalic acid, the simplest dicarboxylic acid, condenses with urea to form *parabanic acid* or *mesoxyl urea*.

BARBITURATES

MALONYL UREA (BARBITURIC ACID)

The more complex dicarboxylic acid, malonic acid, condenses with urea to form the important ureide, *barbituric acid*. Malonic acid may be considered as acetic acid with a hydrogen atom replaced by a carboxyl group. The interaction of urea and the acid forms malonyl urea or barbituric acid, which is a six-membered cyclic ureide, and two molecules of water. Barbituric acid possesses no significant hypnotic properties. However, some of the most important sedative and anesthetic drugs used in medicine today are derivatives of barbituric acid.

RELATIONSHIP OF BARBITURATES TO PYRIMIDINES

The *pyrimidine bases*, uracil, cytosine, and thymine which are found in plant and animal nucleic acids have the same ringlike arrangement of carbon and nitrogen atoms as barbituric acid. These have a different placement of oxygen and amino groups on the pyrimidine ring.

SYNTHESIS OF BARBITURIC ACID

Since barbituric acid forms the basis of many widely used, important hypnotic drugs its synthesis merits detailed consideration. Malonic acid may be prepared by allowing monochloracetic acid to react with sodium cyanide. The cyanide radical replaces the halogen to form cyanacetic acid:

$$CH_2ClCOOH + NaCN$$
$$\rightarrow CH_2CNCOOH + NaCl$$
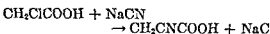
Cyanacetic acid is boiled with alkali and converted to the dicarboxylic acid and ammonia:

$$CH_2CNCOOH + 2H_2O$$
$$\rightarrow CH_2(COOH)_2 + NH_3 \uparrow$$
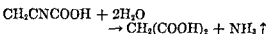
The cyanide radical, therefore, gives rise to the second carboxyl group. The reaction illustrates the classical method for adding carbon atoms or a carboxyl group to an organic compound. The malonic acid is then converted to diethyl malonate because malonic acid is not as stable as the ethyl ester. The *malonic ester* reacts with urea in the presence of alcohol and sodium ethylate to form barbituric acid and ethyl alcohol.

MOLECULAR CONFIGURATION
OF BARBITURATES

The malonyl urea ring is numbered from the lower nitrogen atom in a counterclockwise direction (page 368). The hydrogen atoms on the nitrogen atoms in position 1 and 3 are referred to as *imide* hydrogens. For this reason barbituric acid is often referred to as a diimide. The acidic properties characteristic of barbiturates are due to the imide hydrogens. Barbituric acid and its derivatives exhibit tautomerism and exist in two forms—the *keto* form, represented by the structure on page 268, and the *enol* form. In the enol form one imide hydrogen migrates to the adjacent carbon group. An unsaturated linkage develops between one nitrogen atom and the carbon 2 (see Chap. 9). The hydrogen forms a hydroxyl with the oxygen in the urea residue. Barbiturates stabilize to the enol form by resonance of the pyrimidine ring.

TABLE I.19

BARBITURATES—CHEMICAL TYPES
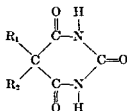
Ordinary or "Oxy" Barbiturates
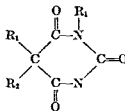
N-Substituted "Oxy" Barbiturates
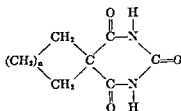
Spirobarbiturates
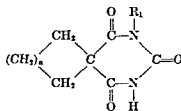
N-Substituted Spirobarbiturates
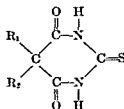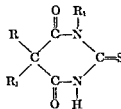
Thiobarbiturates

N-Substituted Thiobarbiturates
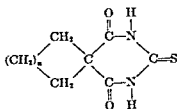
Spirothiobarbiturates
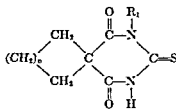
N-Substituted Spirothiobarbiturates
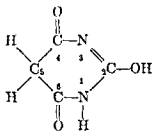
ACIDIC PROPERTIES

The hydrogen of the hydroxyl group which results from the migration of the hydrogen from the nitrogen is acidic in nature. The electron attracting properties of the two nitrogen atoms greatly increase the acidity of the C—OH group. The compound dissociates in aqueous solution into a hydrogen ion and barbiturate ion. Barbituric acid is even

stronger than acetic acid. The acidic hydrogen may be replaced by alkaline metals, such as sodium, potassium or calcium to form salts.

Positions 4 and 6 are occupied by oxygen atoms (carbonyl groups) which are the residue of the original carboxyl groups of malonic acid. Neither of these carbonyl groups is replaced by radicals in barbiturates. The hydrogen atoms on the carbon atom in position 5 are important since they are consistently replaced

by alkyl, aromatic and heterocyclic groups. Such replacements form a host of compounds, many of which possess hypnotic properties.

PREPARATION OF BARBITURATES

The preparation of substituted malonyl ureas (on position 5), is accomplished by allowing malonic ester to react with alkyl halides. This yields the desired radical on carbon 5. The ester first reacts with ethyl bromide, for example, when an ethyl radical is desired. Then another alkyl halide is used. The first hydrogen is replaced by the ethyl radical If the methyl butyl radical is desired, as for example to form pentobarbital, methyl butyl bromide would be used. The reactions are represented as follows:

The substituted malonic ester is then allowed to react with urea in alcohol and sodium ethylate. A substituted cyclic structure then forms. The reaction is represented at the bottom of this page.

RELATIONSHIP OF PHARMACOLOGIC ACTIVITY TO CHEMICAL STRUCTURE

Potency varies with chemical structure. If one hydrogen atom on position 5 is replaced by a methyl group, methyl
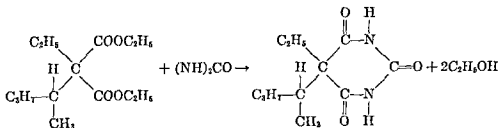
malonyl urea forms. The compound possesses very little hypnotic activity. The dimethyl substitution, likewise, is feebly hypnotic. Although one ethyl and one methyl group increase the potency, the compound is still weakly hypnotic. When two ethyl groups are substituted, *diethyl barbituric acid,* or *barbital,* forms. This is sufficiently potent for clinical use. Barbital was first prepared by Conrad and Guthzeit in 1882 but was not used as a hypnotic until rediscovered by Fischer and Dilthey in 1903. These latter workers conducted extensive syntheses with barbituric acid. As the number of carbon atoms in the substituting groups on 5 position increases, the potency of the resulting barbiturates increases. The compounds which have proved to be the most useful have a total of seven or eight carbon atoms on the 5 position. As a rule, a compound with a short and long chain, as for example an ethyl and an amyl radical, is more potent than one with two medium length chains, as for example a propyl and butyl. Potency invariably increases with an increase in molecular weight regardless of the arrangement of radicals. Toxicity parallels potency. In other words, the margin of safety does not decrease as potency increases. However, beyond a molecular weight of 250, toxicity begins to increase out of proportion to clinical efficacy and the margin of safety becomes narrowed. Generally, as potency increases duration of action is shortened.

OTHER TYPES OF BARBITURATES

Besides the ordinary barbiturates referred to as oxybarbiturates, other types may be formed. Substituted ureas may be used in the condensation. This gives rise to N-substituted ureas. Thiourea

may be used instead of urea to form thiobarbiturates, as may substituted thiourea to give N-substituted thiobarbituric acid. Several thousand compounds are thus possible which fit into the general class of barbiturates. Of these several hundred have been prepared of which only several dozen are useful clinically.

NOMENCLATURE

Barbiturates are named according to the group substituted on the ring. Inasmuch as two substituents may appear on carbon 5, one substituent has placed before it the number 5 indicating its location on carbon 5, and the other 5', indicating that the substituent occupies the other position on carbon 5. Thus, barbital is referred to as 5-5' diethyl barbituric acid. Sometimes the term malonyl urea is used instead of barbituric acid. The generic names of barbiturates of all types have the suffix "al." The ordinary or "oxy" barbiturates are named with a prefix suggesting the name of the most prominent aliphatic radical on carbon 5 on the word barbital. For example, amobarbital (Amytal) has an isoamyl group and an ethyl group; pentobarbital a 5 carbon (methyl butyl radical) and an ethyl radical. The 5 carbon radical is used to name the compound.

VARIATION IN POTENCY DUE TO DIFFERENT TYPES OF RADICALS

ALKYL RADICALS

The radicals on carbon 5 of the clinically useful barbiturates are largely of the *aliphatic* type.

AROMATIC

Aromatic substituents appear infrequently. Phenobarbital, or 5-5' ethyl phenyl barbituric acid is the most im-
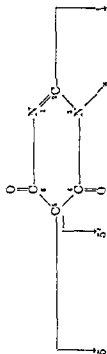
Common Names	Generic Names	Type				
Medinal, veronal, barbitone	Barbital	Long acting, M.P. 190° C.	C_2H_5— Ethyl	C_2H_5— Ethyl	—H	—OH, —ONa
Luminal, cardena, phenobar-bitone	Phenobarbital	Long acting M.P. 177°	C_2H_5— Ethyl	Phenyl	—H	—OH, —ONa
Iprol, probarbitone	Probarbital	Intermediate acting M.P. 203°	C_2H_5— Ethyl	CH_3—CH—CH_3 Isopropyl	—H	—OH, —ONa
Neonal, sonery l, etoval, buto-barbital	Butethal	Intermediate acting M.P. 127°	C_2H_5— Ethyl	CH_2—CH_2—CH_2—CH_3 n. butyl	—H	—OH, —ONa
Dial, trillian, diadol	Allobarbital	Intermediate acting M.P. 171-173	H_2C—CH—CH_2— Allyl	H_2C—CH—CH_2— Allyl	—H	—OH
Allurate, numey l, allylpropnal seonal, siproid	Aprobarbital	Intermediate acting M.P. 141-142	H_2C—CH—CH_2— Allyl	CH_3—CH—CH_3 Isopropyl	—H	—OH, —ONa
Butobarbital, buitsol, butas-paral, nervan	Butabarbital	Intermediate 105-168°	C_2H_5— Ethyl	CH_2—CH_2—CH— CH_3 Sec. butyl	H	OH
Sandoptal	Isobarbital	Short acting M P 139°	H_2C—CH—CH_2— Allyl	CH_3—C—H CH_3 Isobutyl	—H	—OH, ONa

TABLE II.10—Cont.

Common Names	Generic Names	Type				
Ortal	Hexethal	Short acting M.P. 122–125	CH₃ Ethyl → CH_3— Ethyl	CH₃—(CH₂)₅—CH₃ n Hexyl	—H	—OH
Pernoston, pernocton, sonbutal	Butallylonal	Short acting M.P. 133°	CH₃—CH₂—CH₂— CH₃ Sec Butyl	CH₂—C—CH₂— Br β Bromallyl	—H	—OH, ONa
Nostal, noctal, nostral	Propallylonal	Short acting 177–179	CH₃—CH—CH₃ Isopropyl	CH₂—C—CH₂ Br β Bromallyl	—H	—OH, ONa
Rectidon, recton, sigmodal, R289		Short acting 161–163°	CH₃—CH₂—CH₂—CH CH₃ Sec-amyl	CH₂—C—CH₂ Br β Bromallyl	—H	—OH, ONa
Phanodorn, namuron, prosonyl, sonoform, palinum	Cyclobarbital	Short acting M.P. 171–174	C₂H₅ Ethyl	H₂C—CH H₂C C—C H—C—CH₂ Cyclo hexenyl	—H	—OH, ONa
Gemonil	Metharbital	Long acting	C₂H₅ Ethyl	C₂H₅ Ethyl	CH₃	—OH, ONa
Cyclopal		Short acting 139–140°	CH₂=C—CH₂ H Allyl	H H₂C—C C—C H₂C—C H₂ Cyclo pentenyl	H	OH

TABLE II 19—Cont.
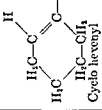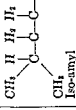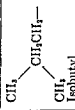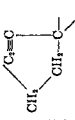
Common Names	Generic Names	Type				
Amytal, somnal dormytal, iso-mytal, pentinal	Amobarbital	Short acting M.P. 153–155	C₂H₅ Ethyl	CH₃—CH—CH₂—C—C— ... CH₃ Iso amyl	H	OH, ONa
Sopartal, sagatal, barbpental nembutal, embutal, pentyl, pentone	Pentobarbital	Short acting M.P. 130	C₂H₅ Ethyl	H₃C—C—C—C—C—CH₃ ... Methyl butyl	H	OH, ONa
Seconal, quinalbarbitone	Secobarbital	Short acting 100°	CH₂=CH—CH₂— Allyl	CH₃—CH₂—CH₂—CH— ... CH₃ Sec. amyl	H	OH, ONa
Delvinal	Vinabarbital	Short acting 161–163	C₂H₅ Ethyl	CH₃—C—C—C—C— ... CH₃ Methyl butenyl	H	OH, ONa
Lotusate, butalbital	Talbutal	Short acting 115°	CH₂=CH—CH₂— Allyl	CH₃—CH₂—CH₂—CH₂— ... CH₃ Sec butyl	H	OH, ONa
Eunarzon	Pronarzon		CH₂—C—CH₃ Isopropyl	CH₂—C—CH₂— ... Br β Bromallyl	—CH₂	—OH, ONa
Metanal, phemilone, isonar Prominal	Mephobarbital	Long acting M.P. 176°	C₂H₅ Ethyl	Phenyl	—CH₂	—OH, ONa

TABLE II.10—*Cont.*

Common Names	Generic Names	Type			—CH₃ Methyl	—OH, ON
Sonnalert, sombulex hexenal Eorpal, tvjnan citopan, cyclonal, dorleo	Hexobarbital	Ultra short acting M.P. 143–145	CH₃— Methyl	$H_2C-C-C=C$ / H / H_2C-CH_2 Cyclo hexenyl	—CH₃ Methyl	—OH, ON
Thioethamyl	Thioamobarbital	Ultra short acting	CH₃— H H₃ / ...-C-C-C / CH₃ Iso-amyl	C₂H₅— Ethyl	—H	—SH, SNa
Thio pento barbital Pentothal	Thiopental	Ultra short acting M.P. 135–159	CH₃—CH₂—CH₂CH— / CH₃ Methyl butyl	C₂H₅— Ethyl	—H	SH, SNa
Kemithal, Thialbarbitone intrameuron	Thialbarbital	Ultra short acting	CH₂=CH—CH₂— Allyl	CH—CH / CH₂ ... / Cyclohexenyl	H	—S—H, SNa
Surital Thioseccobarbital	Thimylal	Ultra short acting	CH₂=CH—CH₂— Allyl	CH₃—CH₂—CH₂—CH— / CH₃ Sec Butyl	H	—SH, —SNa
Neraval Thiogenal	Methural	Ultra short acting	CH₂—S—C₂H₅— Methyl thioethyl	CH₃—CH₂CH₂—CH₂— Butyl	H	SH, SNa
Baytinal Transithal	Buthalitone	Ultra short acting	CH₂=CH—CH₂— Allyl	CH₃ / CH₂—CH / CH₃ Isobutyl	H	—SH, —SNa
Brevital	Methohexital	Ultra short acting	CH₂=CH—CH₂— Allyl	C≡C / CH₃—C— / H₃ 2 Pentynl	CH₃	OH, ONa

portant aromatic substituent. Two phenyl groups substituted on the 5-5' position render a compound ineffective as a hypnotic. The intervention of a carbon atom between the phenyl and 5 carbon (for example, the benzyl group, which is directly attached to the 5 carbon) produces compounds which have convulsive properties. It is possible by making slight changes in some barbiturates to produce convulsants instead of depressants.

BRANCHING OF CHAINS

Barbiturates whose alkyl radicals are derived from secondary alcohols are more potent than those having substituents derived from primary alcohols. Pentobarbital and amobarbital are isomers, each having an ethyl and an amyl group on carbon 5. The five carbon radical in pentobarbital is derived from the secondary alcohol, methyl butanol,

$$
\begin{array}{c}
\text{H} \\
| \\
\text{C}_3\text{H}_7\!\!-\!\!\text{C}\!\!-\!\!\text{OH} \\
| \\
\text{CH}_3
\end{array}
$$

That in amobarbital (Amytal) is derived from the primary alcohol, isoamyl alcohol:

$$
\begin{array}{c}
\text{CH}_3 \quad \text{H} \quad \text{H} \quad \text{H} \\
\hspace{1.2cm} | \quad | \quad | \\
\hspace{0.9cm}\text{C}\!\!-\!\!\text{C}\!\!-\!\!\text{C}\!\!-\!\!\text{OH} \\
\hspace{1.2cm} | \quad | \quad | \\
\text{CH}_3 \quad \text{H} \quad \text{H} \quad \text{H}
\end{array}
$$
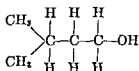
Pentobarbital has twice the potency of amobarbital. The secondary alkyl group also possesses an *asymmetric carbon* atom and, therefore, confers optical activity to the compound (Chap. 9). Branching the chain increases the potency. Thus, amobarbital is more potent than the compound having an n-amyl radical.

UNSATURATION

One or both radicals may be unsaturated in which case potency is enhanced. The vinyl group, $H_2C = CH-$ and the butenyl group, $H_2C = CH - CH_2 - CH_2-$ are less prominent than the allyl group, $H_2C=CH-CH_2-$. Two allyl groups on carbon 5 results in dial (5-5' diallyl barbituric acid). Unsaturation in a cyclic radical likewise increases potency. Cyclohexenyl substituents are more potent than cyclohexanyl.

HALOGENATION

Halogenation of alkyl radicals also increases potency and intensity of action Bromine is the halogen most often found. Compounds containing chlorine have not been found clinically useful thus far. The halogen atoms usually appear on one but may be placed upon both 5-5' substituents. *Pernoston*, which is 5-5' butyl-β-bromoallyl barbituric acid, is the most familiar of these. The halogen does not enter directly into the pyrimidine ring nor does it replace any group on the ring of the barbituric acid.

ALICYCLIC RADICALS

An alicyclic group may replace a hydrogen atom on the 5 carbon position. Such a substitution gives rise to compounds which are more potent than those which have a like number of carbons arranged in a chain. An example of a barbiturate with alicyclic radicals is cyclohexenyl-ethyl barbituric acid, or *phanodorn*.

SPIROBARBITURATES

The two substituents on carbon 5 may be arranged to form a ring. Carbon 5 then is common to both rings, the pyrimidine and the substituent. A series of

such compounds consisting of spiro-hexanes, spiropentanes, spirobutanes and spiropropanes have been prepared which possess hypnotic activity. Anesthetic effects were noted when two substituents were introduced into the spirohexane, butane and pentane rings. However, side actions were encountered so they have never gained widespread usage. Spiro-barbiturates have also been prepared with thiobarbituric acid. (Table I.19)

N-SUBSTITUTED BARBITURATES

One imide hydrogen (on position 1 or 3) may be replaced by an alkyl group. The resulting barbiturate is referred to as a nitrogen (N-) substituted compound, since the replacing group is on a nitrogen atom of the urea residue. Such compounds are synthesized by using methyl or ethyl ureas. Other substituents could be used but the N-methyl derivatives are the most suitable of this

enyl-methyl barbituric acid. N-methyl barbiturates of high molecular weight, as will be discussed later, are classed as ultra short-acting compounds. The number of N-methyl derivatives which have been prepared and investigated experimentally to date for clinical purposes is limited. N-methyl barbiturates tend to manifest neuromuscular activity probably due to a central excitant effect. The presence of the radical on the nitrogen atom tends to shorten the action. As the group lengthens stimulation becomes apparent. Alkylation of both the 1 and 3 positions results in convulsants.

THIOBARBITURATES

Sulphur replaces oxygen in many organic components. In urea, such a replacement results in thiourea. The use of thiourea in the condensation with malonic acid gives rise to a series known as *thiobarbiturates*.
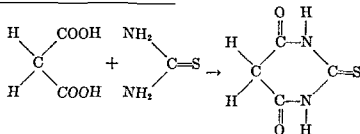
series, clinically speaking. N-substituted barbiturates have, in addition to the aliphatic radical on the nitrogen, two substituents on the 5 position. Thus, three alkyl groups are present on the ring. As is the case with other barbiturates the potency of N-methyl barbiturates increases with the molecular weight. The best known and one of the earliest to be introduced of the N-substituted barbituric acids is hexobarbital (Evipal). The chemical name is N-methyl-cyclohex-

Thiobarbituric acid (thiomalonyl urea) has identical replaceable atoms and gives rise to a series of compounds similar to the barbiturates. Both hydrogen atoms in the 5 position are replaced by aryl, alkyl, or cyclic radicals. The thiobarbiturates, like the oxybarbiturates, possess narcotic potency. Fischer and Dilthey were also the first to study the thiobarbiturates. However, they prepared the diethyl and other low molecular weight derivatives and found them

to be toxic. Therefore, they discontinued further study. Nothing further was done until interest in these compounds were revived in the early 1930's when higher molecular weight derivatives were synthesized. These are more potent and less toxic than the lower molecular weight structures.

A number of thiobarbiturates have been prepared which are effective for clinical use. The most important of these are thiopentobarbital (thiopental), thiamylal (Surital) and allyl-cyclohexenyl thiobarbituric acid (Kemithal). Thiopental (Pentothal) is the thio analogue of pentobarbital (Table II.19). Thiamylal (Surital) is the thio counterpart of secobarbital. *Thioethamyl*, or isoamyl-ethyl-thiobarbituric acid, is the analogue to isoamyl-ethyl-barbituric acid, or amytal. The replacement of oxygen by sulphur increases narcotic potency. The position of the sulphur is indicated by placing a 2 before the prefix thio. It would be possible for the sulphur to be on the 4 or 6 position since these also are occupied by oxygen atoms. Thio derivatives are rapid acting drugs.

SYNTHESIS OF THIOBARBITURATES

The formation of thiobarbiturates is accomplished by condensation of thiourea with malonic acid. The synthesis is carried out in the same manner as that of oxygen analogues except that thiourea is used instead of urea. Thiourea is refluxed with the desired alkyl-substituted malonic ester in an alcoholic solution of sodium ethylate to form the substituted thiobarbituric acid.

PHARMACOLOGIC TYPES OF BARBITURATES

Barbiturates are usually classed from a pharmacologic standpoint as long act-

ing, intermediate acting, short acting and ultra short acting according to their potency and duration. Relationships of potency to chemical structure have already been alluded to and are summarized in Table II.19.

CHEMICAL PROPERTIES OF BARBITURATES

The oxygen analogues of barbiturates are bitter tasting white crystals or powders. Solutions are colorless. Barbiturates are sparingly soluble in water. Aqueous solutions are acid to indicators. Barbiturates form salts with bases of sodium, potassium or calcium hydroxide. The salts of barbiturates are more soluble in water than are the acids. The acid form of a barbiturate is soluble in organic solvents, such as chloroform, benzine, alcohol and ether. The sodium salts of barbiturates are salts of weak acids and strong bases. They hydrolyze, therefore, in water to form highly alkaline solutions. Solutions of sodium salts have a pH between 9 and 11. Barbital, if combined with an acid, may be used as a buffer in chemical analytical procedures.

The thiobarbiturates are yellow tinted hygroscopic powders with a bitter taste They too form sodium salts which are soluble in water, highly alkaline and insoluble in organic solvents, such as benzine and ether. The free acid is easily precipitated from solutions of salts by most acids. Even a feeble acid, such as carbonic acid precipitates the base. Sodium carbonate (5%) is added to thiopental to afford some buffering action and to prevent the free acid from precipitating in aqueous solutions by atmospheric carbon dioxide. Carbon dioxide in fact is used to precipitate the acid during preparation for purification.

STABILITY

Barbiturates are stable in the dry form. They are not stable when exposed to air or heat or light. Most barbiturates are hygroscopic and absorb moisture from the air which hastens their decomposition. Preservation is best accomplished by storing in sealed ampules, dark bottles, or colored capsules. *Solutions of barbiturates* are unstable and decompose rapidly upon standing. Boiling an aqueous solution quickly converts the barbiturate to ammonia, carbonic acid, and other nitrogen containing compounds. The resulting by-products vary with temperature, concentration of the drug, alkalinity and so on. Changes occur gradually when a solution is allowed to stand for some time. Solutions of barbiturates must be freshly prepared using sterile powder and water. They cannot be sterilized by boiling.

Barbiturates whose alkyl substituents are derived from primary straight chain alcohols hydrolyze upon heating and standing more rapidly than those having alkyl groups derived from secondary alcohols. The sodium salt of diethyl barbituric acid (Barbital) in aqueous solution is 85% hydrolyzed in sixteen hours at 100°C. Barbiturates whose alkyl groups are derived from secondary alcohols are only 25% hydrolyzed over the same time interval. The products of hydrolysis of barbital have been identified as diethyl-acetyl urea, urea, carbon dioxide, ammonia, sodium carbonate, sodium bicarbonate, sodium diethyl acetate, and sodium diethyl malonate.

Barbital may be sterilized by combining it with 95% of the calculated amount of sodium hydroxide necessary to convert it to the sodium salt. The solution is then heated to 100°C. for the necessary sterilization period. Only slight decomposition occurs. The excess acid is filtered off and the solution is stored in sterile ampules for use for subcutaneous injection. Higher molecular weight barbiturates decompose if boiled or treated in this manner, however. Propylene glycol (10%) is used as a solvent for pentobarbital. Secobarbital is dissolved in polyethylene glycol (MW 300) to form a stable solution. Halogenation of the aliphatic substituents of barbiturates does not confer increased stability. Thiobarbiturates in the powder form stored in sealed ampules filled with nitrogen keep indefinitely. A 5% solution of thiopental deteriorates steadily at room temperature of 18°C. to 22°C. as determined by verifying the melting point of the extractable thiopental. Refrigeration at 5°-6°C. reduces the rate of deterioration. The variations in melting point increase as turbidity of the solution increases. It is felt that solutions should not be used after three days if stored at 18°C. and seven days at 5°-6°C.

No correlation has been noted between the rate and degree of hydrolysis of sodium salts of a barbiturate and the onset and duration of anesthesia. Likewise, no correlation exists between the onset or duration of anesthesia and the salt/acid ratio at the pH for this ratio.

PHYSICO-CHEMICAL PROPERTIES AND NARCOTIC POTENCY

There is some correlation between hypnotic efficiency of a barbiturate and certain physico-chemical properties, such as surface tension effects and adsorbability.

ADSORPTION

Barbiturates are readily adsorbed on surfaces of activated charcoal and other

adsorbing substances. Tabern and Vol-willer demonstrated that barbiturates were adsorbed by activated charcoal. They observed, however, that adsorption is not quantitative. In a series of the commonly used barbiturates 79% to 96% of the amount dissolved in 300 cc. of a 0.12% solution was adsorbed. Adsorption has been utilized to recover barbiturates from aqueous solutions for analysis. Since adsorption is not necessarily complete, the value of this technique for quantitative analysis is questioned.

EFFECT ON SURFACE TENSION

The ability of barbiturates to lower the surface tension of water, the increase in molecular weight and the increase in narcotic potency parallel each other. The surface tension of pure water at 28°C. is 72.78 dynes per cm.^{2} The changes in surface tension produced by certain barbiturates are summarized in Table III.19. Narcotic potency of barbiturates increases up to a molecular weight of 250, beyond which toxicity increases more rapidly than potency. However, the ability to lower surface tension increases with the molecular weight beyond this point of maximum narcotic potency. This

fact casts doubt on the importance of surface tension as a mechanism for production of narcosis by barbiturates.

LIPOID SOLUBILITY

Barbiturates possess varying degrees of lipoid solubility, though they do not follow the Overton Meyer rule (Chap. 27). The thiobarbiturates are more soluble in lipoids than the oxybarbiturates (Table IV.19). The oil-water partition coefficient for thiopental is 4.7, that of amobarbital 2.9 and that of barbital 0.214. Penetration into the brain (passage through the blood brain barrier) is closely allied to lipoid solubility. The more soluble in lipoids the more rapid the penetration appears to be.

DISTRIBUTION IN TISSUES

Barbiturates in general are distributed in all tissues of the body in a rather uniform manner. The distribution, to a certain extent, varies with the type of barbiturate. After an intravenously administered dose, a barbiturate disappears from the blood almost completely. However, very minute, almost undetectable amounts circulate there for some time. The rate of disappearance varies with the size of the dose and structure of the molecule of the barbiturate used. The rate of disappearance is inversely pro-

TABLE III.19

EFFECT OF CERTAIN BARBITURATES UPON THE
SURFACE TENSION OF WATER

	Dynes per sq. cm.	% of That of Pure Water
Diethyl Barbituric Acid.....	72 64	99.7
Sodium Diethyl Barbiturate.	72 40	99 5
Pento Barbital	70.64	96.9
Sodium Pento Barbital	69.38	95.2
Iso Amyl Ethyl Barbituric Acid.........	61.36	84.3
Sodium Iso Amyl Ethyl Barbituric Acid.... .	69.25	95.0
Phenobarbital.....	71.84	98.6
Sodium Phenobarbital	72.54	99.5
Sodium Ortal....	53.06	72.9

TABLE IV.19

DISTRIBUTION OF ULTRA SHORT-ACTING BARBITURATES AND OTHER INTRAVENOUS HYPNOTICS BETWEEN PEANUT OIL AND PHOSPHATE BUFFER AT pH 7.4
(AFTER MARK)

	% in Oil
Hexobarbital (Evipal)	66
Thiopental.	95
Kemithal ..	95
Dolitrone ...	95
Thiamylal....	97
N-methyl thiopental	99+
Methitural...	99.4

portional to the dose. The amount absorbed by a particular tissue is dependent upon the abundance of the blood supply to that tissue. The liver, muscle and various glandular organs remove the bulk of the barbiturates from the blood. This is especially true of barbiturates possessing high molecular weight alkyl substituents.

Barbital injected in both sub-anesthetic and anesthetic doses is equally distributed in all body fluids and throughout various parts of the nervous system. It has been well established that there is no localization of barbiturates in any subdivision of the brain. Koppanyi and Dillie and other workers have shown that the distribution is uniform in all subdivisions of the brain. There is a lag in the uptake of barbiturates by the brain. The longer acting drugs show the greatest period of lag. Thiopental shows the least lag. The peak is quickly attained with thiopental (7 minutes) (Table IV.19). A lag is also noted in cerebrospinal fluid concentrations. It is longest with the long acting barbiturates and shortest with short acting barbiturates, such as pentobarbital. These are found in higher concentration in the nervous system than longer acting drugs, such as barbital. The thiobarbiturates are found in still greater concentrations. These disappear from the tissue in a shorter time interval. This initial high concentration accompanying rapid acting drugs and the rapid disappearance are believed to explain the long and short action of these substances. The brain retains barbiturates longer than other tissue and apparently exerts less destructive action upon them than other tissues. This may be due to binding of the drug to the protein. Five per cent or more thiopental is bound to the protein of the brain.

With the exception of barbital and phenobarbital, equilibrium between brain and blood is rapidly established with most barbiturates. Short acting barbiturates pass into the brain with greater rapidity than longer acting. When long acting barbiturates, such as phenobarbital and barbital, are administered the brain concentration rises gradually. As the concentration increases the neurologic effects progressively increase. Ample evidence exists that the lag in onset or latent period noted with barbiturates is due to the ease with which they penetrate the so-called blood-brain barrier. Ultra short acting barbiturates, particularly thiobarbiturates were observed by Brodie, Mark and their associates to pass rapidly across the blood-brain barrier and to have a high uptake by the body fat. The rapid onset of action is due to the ease with which the drug enters the brain. The plasma concentration falls rapidly for the first 15–30 minutes after a single intravenous injection of thiopental after which the decline is gradual. The maximum tissue concentration is reached within one minute after injection and thereafter declines at a rate parallel to the plasma level in all tissues except muscle and fat. The muscles attain equilibrium within fifteen minutes after injection. The maximum deposition in adipose tissues occurs

TABLE V.19

BRAIN/PLASMA CONCENTRATION OF INTRAVENOUS
BARBITURATES IN DOGS ONE MINUTE
AFTER INJECTION

Thiopental..........	1.1
Thiamylal...........	1.2
Kemithal.............	1.15
N-methyl thiopental.	1.7
Hexobarbital.........	1.0
Dolitrone...........	1.32
Methitural...........	0.90

TABLE VI.19

LOCALIZATION OF INTRAVENOUS ANESTHETICS IN PERIRENAL AND OMENTAL ADIPOSE TISSUE (TISSUE CONC./PLASMA CONC.)

Hexobarbital (Evipal).	3.5
Kemithal	8.0
Thiopental	12.0
Dolitrone.	12.0
Thiamylal..	15.0
N-methyl thiopental	25.0
Methitural.	18.0

within 1½-hours (Table VI.19). It is not complete until approximately four hours later. After an initial injection which establishes equilibrium with most tissues, removal of the drug from the blood stream depends upon the diffusion into fat which is slow, comparatively speaking, or by detoxification. The period of narcosis is increased out of proportion to the increase in dosage. Cumulative effects then appear, characterized by a delay in recovery. The initial short action is due to the rapid uptake by the tissues. Large doses produce prolonged depression since equilibrium is attained between the plasma, brain and body tissues. The rate of metabolism is slow (10–12% per hour). Analysis of the fat depots in the perineural, omental and lumbar dorsal depots reveal concentrations 3½–25 times the plasma level. Muscle and other tissues contain only ¾–1½ times the plasma level. Lipoids after equilibrium contain 50 times as much as muscle. Other thiobarbiturates and hexobarbital behave similarly. The arterial blood contains slightly more than the venous blood.

PROTEIN BINDING

Barbiturates become bound to the blood proteins when injected intravenously. The binding appears to be most pronounced with the albumin fraction of the plasma protein. The binding is re-

versible and dependent upon the albumin and the drug concentration in the ultrafiltrate. Compounds having alkyl radicals of four or five carbon atoms are bound more strongly than those with shorter chains. The thio analogues are more strongly bound than the oxy members. As much as 60–70% thiopental is adsorbed to the plasma proteins. Both bovine and human serum bind barbiturates. The degree of binding varies with the pH. It becomes maximal at pH 8.0 for most barbiturates. The disappearance of barbiturates from blood was mistakenly ascribed to rapid destruction since, for many years, protein binding was overlooked.

ELIMINATION OF BARBITURATES

Barbiturates are non-volatile substances. They are, therefore, eliminated either unchanged by the kidneys, gastrointestinal and sweat glands or they undergo biotransformation and lose their identities.

Long acting barbiturates, such as barbital and phenobarbital, are excreted unchanged into the urine. Others undergo varying degrees of change in the body. In general, barbiturates having less than three carbon atoms on the alkyl side chains are apt to be excreted unchanged. Derivatives having longer alkyl side chains are metabolized partly or completely. The drug appears in the urine in traces after ordinary doses. After oral ingestion barbital continues to be eliminated in small quantities over a period of several days. As much as 90% of a therapeutic dose may be recovered in the urine of animals in a five to seven day period. The rate of elimination and quantity excreted vary widely with dosage, mode of administration, method of extraction,

species under study and with the technique of analysis. The slow elimination of the long acting barbiturate is explained by the fact that it is retained in nerve tissue. Phenobarbital is also recovered in the urine although in lesser quantities than is barbital. Four and one-half to 24% of the allyl isopropyl barbituric acid was recovered in the urine in three days. Quantities up to 30% of diallylbarbituric acid (Dial) were recovered. On the other hand, bromallyl isopropylbarbituric acid (Pernoston) and isoamylethylbarbituric acid (Amytal), which are shorter acting derivatives, are not recovered in the urine after therapeutic doses. Traces of metabolic products indicating biotransformation may be detected, however. Twenty per cent of an ingested dose of Peroston is recovered in urine as an acetonyl barbituric acid. Thus, the generalization may be made that intermediate acting compounds are partly destroyed while the short acting are detoxified completely. Massive doses do, however, appear in the urine. Less than 1.5% thiopental appears in the urine.

REACTIONS INVOLVED IN DETOXIFICATION

The metabolism, biotransformation, distribution and excretion of barbiturates has been followed in recent years by the use of radioactive isotopes. Thiopental and other thiobarbiturates are studied using radioactive sulphur (S^{35}) in the thiourea residue of the barbiturate. The oxygen analogues have been studied using N^{15} in the urea residue.

In general four types of reactions appear to be involved in the transformation. These are (1) oxidation of the radicals in position 5, (2) loss of the N-alkyl radicals, (3) removal of sulphur from the thiobarbiturate and (4) disruption of the pyrimidine ring by hydrolysis. The most

important of these is oxidation of the radicals in position 5. Pentobarbital, for example, appears to be converted, in part, to a hydroxy derivative. Propallylonal forms a keto derivative. Thiopental is oxidized to a carboxylic acid. The carboxyl group is on the terminal carbon of the methyl butyl side chain:
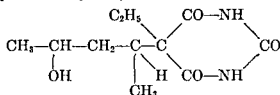
Brodie found 15% of a dose appeared in this form in the urine. Butisol is detoxified in a like manner. Propallylonal forms a keto derivative. Thiopental is oxidized to a carboxylic acid. The carboxyl group is on the terminal carbon of the methyl butyl side chain:
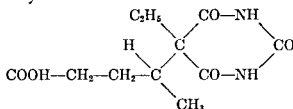
The resulting hydroxy keto and carboxy derivatives are non-hypnotic.

The N-alkyl barbiturates are detoxified by demethylation. N-methyl phenobarbital is partly converted to pentobarbital by demethylation. This is an example where both the metabolite and the parent compound exert a hypnotic effect.

The sulphur atom of thiobarbiturates is to a certain extent removable so that the compound is converted to an oxybarbiturate. Thiopental is thus converted into phenobarbital. Studies using radioactive sulphur indicate 90% urinary excretion of the sulphur. Some of the sulphur is converted to inorganic sulphates, some to an organic, chloroform soluble substance and the remainder into an unidentifiable portion.

Ample evidence exists that disruption of the pyrimidine ring occurs by hydrolysis. Thiourea is found in the urine

after injection of thiopental and other barbiturates. Amobarbital undergoes disruption of the ring. It has been shown to break down first to isoamylethylacetyl urea. This is then converted by oxidation to isoamylethyl acetamide and then to isoamylethylacetic acid. These products may be recovered in the urine. However, portions of these byproducts are converted by oxidation ultimately to carbon dioxide and water. Ultra short acting and short acting barbiturates are not ordinarily detected in the urine of man or animals following ingestion of therapeutic doses. When massive doses are administered, however, most of the oxygen analogues appear in the urine. The ultra short acting thiobarbiturates and the N-methyl type do not. Presumably this is due to their retention by body fat and slow release for metabolism. While barbital and therapeutic doses of long acting barbiturates are recovered in urine almost quantitatively, massive doses are not. When four or five times the therapeutic dose of barbital is administered only 40% to 50% of the total amount appears in urine. Apparently the body is capable of transforming barbital also, particularly when given in large amounts.

RENAL THRESHOLD

It has been suggested that a renal threshold exists for barbiturates. The drugs do not pass into the urine if the plasma concentration is low. The larger, heavier molecules of the oxygen analogues, the N-methyl compounds and the thiobarbiturates are more soluble in lipoid than the lighter molecules. In vitro studies using vegetable oils show moderate absorption (66%) of the oxybarbiturates. The thiobarbiturates are 95%–100% absorbed. Consequently they are more rapidly removed from the blood so that the level does not attain the threshold value. When larger doses are given the blood level exceeds the theshold level and the drug then appears in the urine. Barbital possesses a low molecular weight and leans toward poor lipoid solubility. It is distributed equally between the body fluids and tissues and presumably has a low threshold. Traces of amytal and pentobarbital appear in the stools and sweat. Studies using radioactive sulphur indicate that less than 5% of thio derivatives appear to pass into the feces.

ROLE OF THE LIVER IN DETOXIFICATION

The greater portion of a barbiturate is metabolized by the liver. Pratt first, and later others, showed that short acting barbiturates cause prolonged hypnosis when administered to animals with liver injury. Duration of action of the long acting type was not influenced by hepatic dysfunction. The duration of hypnosis of short acting barbiturates, on the other hand, was uninfluenced by bilateral nephrectomy, or when experimental nephritis was induced in the animals. Hypnosis was prolonged when a long acting barbiturate, as for example, barbital was administered in the presence of renal damage. After ligation of the portal vein or hepatic artery of dogs to eliminate liver function the period of narcosis following the administration of thiopental is prolonged four or five times. The evidence presented by numerous workers that hepatic dysfunction prolongs the effects of thiopental and other thiobarbiturates is convincing and quite suggestive that the major role in inactivation is played by the liver. The rapid onset of action and short duration of the ultra short acting barbiturates have been ascribed to rapid destruction.

This, as has been previously mentioned, is not the case. The rapid onset of action is due to the ease of passage into the brain and the rapid uptake by tissues. Large doses, however, accumulate in the fat and produce prolonged depression since equilibrium is attained between blood, brain and fat. The rate of metabolism is slow, however. Thiopental, thiamylal and other thiobarbiturates of similar molecular weight are destroyed at the rate of 10-20% per hour. The plasma does not slowly destroy barbiturates. Rapid disappearance from the plasma is accounted for by plasma binding and tissue uptake rather than destruction.

Shideman and his co-workers have studied the enzymes used by the tissues in the detoxification of thiopental. The results of these studies suggest that destruction is not due to a direct action of a particular enzyme. Instead a chain of enzymatic reactions occurs which release sufficient energy to attack the compound. It is not known definitely whether or not the energy utilized for the transformation of thiopental is derived from Krebs cycle oxidations or from high energy phosphate bond compounds resulting from such oxidations.

QUALITATIVE AND QUANTITATIVE ANALYSIS OF BARBITURATES

The qualitative and quantitative analysis of barbiturates in body fluids is occasionally necessary in clinical and in medicolegal problems. Numerous tests of a general nature are available for barbiturates. Many are non-specific. Strongly heating a barbiturate, particularly with an alkali, causes degradation and yields ammonia and other amines which can be identified by odor. This reaction is not specific for identification of barbiturates because it is characteristic of many other nitrogen containing substances.

Barbiturates yield a white, voluminous precipitate when mixed with *Millon's reagent*. This reagent is a mixture of nitrous and nitric acids containing mercuric nitrite and nitrate (usually prepared by dissolving mercury in nitric acid). The precipitate redissolves in an *excess of reagent and a clear solution* forms. Other biological substances chemically related to barbiturates, such as pyrimidines and purines, may give a similar response. The test, therefore, has limited applicability.

Ureides respond to the *murexide* test, but this test, likewise, is not specific since purines and other biological substances also respond to it. The murexide test is performed by evaporating a solution of the suspected substances mixed with an equal portion of concentrated nitric acid on a watch glass over a water bath. A violet coloration results upon application of a drop of concentrated ammonium hydroxide to the residue. Handorf proposed this test for the detection of barbital.

COBALT COLOR REACTION

A widely accepted test for detection of barbiturates employs the so-called *cobalt color reaction*. Cobaltous compounds dissolved in an anhydrous medium form a violet colored organo-metallic compound with barbiturates if the mixture is made alkaline. Zwicker used cobaltous chloride in absolute methyl alcohol as the reagent. The barbiturate, also dissolved in alcohol, is then added and the mixture made alkaline with barium methylate ($BaOCH_3$). Bodendorf used 1% cobaltous nitrate and potassium hy-

droxide in alcohol as the alkalizing medium. Koppanyi used cobaltous acetate in anhydrous methyl alcohol and isopropyl amine to make the mixture alkaline. The interaction is quantitative. The depth of the color varies with the concentration of barbiturate. The colorimeter may thus be used to estimate the barbiturate. There are, however, some drawbacks to the method for quantitative estimation of barbiturates. First, the reaction is not absolutely specific for barbiturates. The color results from the interaction of the imide hydrogen atom of the barbiturate molecule and the cobalt ion. Other biological substances of the purine type, such as uric acid and creatine, creatinine and so on, which possess one or more imide hydrogens, may respond positively. However the test becomes selective for barbiturates at the pH range obtained by using sodium ethylate as the alkalizing agent. The response then is positive only to diimides. Second, the intensity of the color increases as the quantity of cobalt ion and sodium ethylate is increased. A certain point is reached beyond which no further increase in depth of color occurs. The ratio of the cobaltous ion to the diimide substance necessary to produce a maximum of intensity in color is 1 to 8. The combination of the cobalt and the barbiturate is effected through the eight coordinate valences of cobalt. Third, the dispersion medium must be anhydrous, otherwise a precipitate of cobaltous hydroxide occurs. Fourth, the cobalt color reaction is characteristic of all barbiturates and is of no value in differentiating between or identifying individual barbiturates. Barbiturates also form colored complexes with copper salts.

Koppanyi's procedure, which utilizes 1.0% cobalt acetate and 5% isopropyl amine dissolved in absolute methyl alcohol, is the more widely used of the numerous modifications of the cobalt reaction. Twelve cc. of the color free chloroform extract are mixed with 1 cc. of a 0.1 N cobalt acetate solution. This is followed by 1 cc. of 0.6 N isopropyl amine. The color is matched in a colorimeter with standards prepared from known concentrations of the suspected barbiturate. The strength of the standards should approximate concentrations of the unknown. All manipulations should be executed in the same manner and at the same time. The same interval of time should elapse between addition of solutions; otherwise, variations in depth of color may occur or there may be changes in end points.

RESPONSE OF THIOBARBITURATES

Thiobarbiturates respond to aforementioned tests in a similar manner as do the oxygen analogues. Thiobarbiturates produce a green color with the cobalt instead of a violet one if mixed with the cobalt reagents. They also form precipitates with Millon's reagent. Thiobarbiturates decompose to sulphides if boiled with sodium or potassium hydroxide. The presence of the sulphide is detected by acidifying and adding a salt of copper, silver or mercury. A black precipitate of the metal sulphide results.

EXTRACTION FROM TISSUE

Quantitative determinations are frequently sought upon blood, urine, stomach contents and tissues due to the widespread use of barbiturates in medicine and the high incidence of intentional and accidental overdosage. A number of methods for the quantitative extraction of the barbiturate from biological materials are in use. Koppanyi

and his co-workers suggest digesting a weighed specimen of tissue with 5% potassium hydroxide for 24 hours. The proteins are then precipitated with copper sulphate. The mass is then filtered and the barbiturates are extracted from the acidified filtrate with chloroform. Tissues may also be frozen with liquid air, pulverized and treated with acid and the barbiturates extracted with chloroform. Blood may be extracted by precipitating the proteins with sodium tungstate and sulphuric acid. The filtrate is then extracted with ten volumes of chloroform to recover the barbiturate. Large quantities of blood are necessary for accurate results when using this method. The barbiturate may also be adsorbed to activated charcoal from aqueous extracts of tissues. This is in turn mixed with plaster of Paris and then extracted with petroleum ether. The cobalt color test is then applied to these residues, once the extractions have been accomplished. The objection to this technique is that adsorption is not absolutely quantitative.

Unfortunately one is never sure that all the barbiturate is recovered since it may be partially decomposed by the alkali or it may be bound to the protein.

DETERMINATION BY VACUUM DISTILLATION

Barbiturates may be recovered quantitatively by distillation in a vacuum. The drug is first extracted from tissues after acidification with 20% acetic acid. Loss due to destruction of barbiturates is less likely when extractions are carried out using an acid instead of a strongly alkaline medium. Two or three times the volume of acetic acid per volume of tissue is used. The mixture must stand for 24 hours after which proteins are pre-

cipitated by adding sodium tungstate. The filtrate is then extracted with ether. The residue recovered after evaporating the ether is then sublimed under reduced pressure (0.005 mm. Hg). The recovered barbiturate is estimated gravimetrically. The barbiturate may be identified by determining its melting point and confirmation may be made by the method of mixed melting point.

DETERMINATION BY FLUOROMETRY

Solutions of barbiturates absorb ultraviolet light. Analytical methods of identification and quantitative determination are based upon this principle. The wave lengths absorbed depend upon the molecular configuration and the quantity or the amount present. Hellman, Shettles and Stran first applied this principle to the analysis of thiopental. They noted a maximum absorption of ultraviolet light of a wave length of 2880 Å by ether extracts of acidified filtrate of solutions suspected of containing acid thiopental. Barbital, dial, phenobarbital, Nembutal and Evipal showed no significant absorption under similar circumstances.

The test used by these workers is not specific for thiopental, however. The byproducts of metabolic transformation of thiopental have the same absorption characteristics as thiopental. Brodie refined the technique and made it specific by controlling the pH and by using a mixture of hexane and isoamyl alcohol for the extraction of the drug. The free unaltered thiopental may thus be extracted without contamination with the metabolites. The fluorometer may be used for the quantitative determination of barbiturates. Barbiturates may also be identified by using the fluorometer. The absorption spectra shift with changes in pH.

Each barbiturate has a different absorption spectra at two different pH's. No two appear to be alike.

Paper chromatography has also been used for separation and identification of barbiturates (Chap. 28).

MODE OF ACTION

Quastel and his co-workers (1933) presented data which suggested that barbiturates cause an inhibitory effect on oxidative processes of brain and other tissues in vitro (Chap. 27). Since that time additional data has been obtained on this aspect of biochemical activity. Much of the data is in conflict with Quastel's idea. At the present time, therefore, there is no agreement as to the exact site of suppression in the intracellular oxidative scheme. Discrepancies exist between the concentration required to produce the effects on oxidation in vitro and narcosis in vivo. More recent experimental data indicate that barbiturates interfere with the utilization of oxidative energy for synthesis of compounds (ATP, ADP) containing energy rich phosphate bonds (Chap. 27). The narcotic response in vivo is obtained by concentrations less than those necessary to suppress cellular oxidations in vitro.

Miscellaneous Sedatives, Hypnotics and "Tranquilizers"

INERTNESS VERSUS REACTIVITY OF HYPNOTICS

IT HAS BEEN BROUGHT OUT in the preceding chapters that central nervous system depressants fall into two general groups—volatile and non-volatile. Generally speaking the volatile drugs are inert molecules which are non-reactive in the body. The non-volatile drugs on the whole are inclined to be reactive and are subject to modification by biochemical mechanisms. The inert, volatile substances are almost exclusively aliphatic hydrocarbons, ethers, halogenated aliphatic hydrocarbons or inorganic gases. The chemical groupings of the reactive compounds are more varied. Some are aliphatic derivatives while others are cyclic structures. Among the useful aliphatic, non-volatile substances are the alcohols, aldehydes, ketones, esters, halogenated alcohols, halogenated aldehydes and the disulphones. Among the non-aliphatic central nervous system depressants are the nitrogen containing cyclic structures, such as the amides, substituted ureas, the barbiturates and the narcotics. These have been described in the previous chapters. Certain miscellaneous heterocyclic structures not mentioned previously will be described in this chapter.

HYPNOPHORE GROUPS

On inspection of the structural formulae of the majority of non-volatile hypnotics certain specific groupings and structural similarities seem to predominate. A polar group, usually a feeble one, such as a hydroxyl, ketonic or amide, is invariably present. These groupings, since they are believed to be responsible for hypnotic activity, are sometimes referred to as the *hypnophore*, or *anesthesiophore* groups. The suffix "phore" means bearing or carrying. The term *chromophore* applied to dyes refers to the grouping or linkage of a molecule responsible for the coloration of the compound. In the case of hypnotics the hypnophore grouping is believed to be responsible for hypnosis. The presence of groupings commonly associated with hypnosis on a molecule does not necessarily imply that the compound is hypnotic. Their presence on a molecule make hypnosis possible when they coexist with other groupings. The sedative activity of aliphatic alcohols may be correlated with the size of the molecule and with the electrophilic properties of groups alpha to the hydroxyl bearing carbon atom. The molecule is reactive at the hydroxyl group. *This portion is* hydrophilic (lipophobic). The remainder of

the molecule is hydrocarbon in nature. This makes it inert, bulky, and lipophilic (hydrophobic). In the alcohols the reactive group is attached to an electron attracting center surrounded by alkyl groups. A similar arrangement is noticeable among aliphatic aldehydes, ketones and esters. The ketones are much more strongly hypnotic than alcohols. Pronounced branching of the chain or halogenation appears to enhance sedative and hypnotic properties in most cases. The bulky lipophilic portion of the molecule has been referred to as the auxohypnotic group.

Amides, carbamates, ureides and related hypnotics described in previous chapters manifest the same type of structure-activity relationship as the alcohols, aldehydes, ketones and so on. In these the

$$\begin{array}{cc} H & O \\ | & \| \\ -N- & C- \end{array}$$

group appears to be the reactive polar group. The bulky portion of the molecule consists of a hydrocarbon residue also. The radicals on position 5 in the barbiturates are alkyl radicals. As is the case with the aliphatic hypnotics, they add bulk and inertness to the molecule.

MOLECULAR WEIGHT AND POTENCY OF HYPNOTICS

The increase in the number or size of alkyl groups around an electron attracting carbon center enhances hypnotic or narcotic activity, not only in the aliphatic, oxygen and halogen containing compounds, but also in the ureas, carbamates, barbiturates and other derivatives. In the aliphatic disulphones (Sulphonal series, Chap. 17) the

$$\begin{array}{cc} | & \| \\ -C-O-S-OH \\ | & \| \end{array}$$
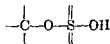
is the active group while the methyl ethyl substituents are the inert, bulky portion. The tetramethyl derivative is inactive. The dimethyl ethyl homologue (sulphonal), the higher molecular weight homologue with three ethyl groups (trional) and the homologues with four ethyl groups (tetronal) are increasingly active. Among the urethanes (Chap. 19) derived from aliphatic alcohols, ethyl carbamate is feebly hypnotic. Hedonal, derived from tertiary amyl alcohol and aponal, derived from secondary amyl alcohol have alkyl substituents of greater carbon content and, therefore, have profound sedative activity. The features which seem to be essential for hypnotic activity are branched chains, halogens or unsaturation in the portion of the molecule adjacent to the polar group. Alkyl groups are electron attracting. Double bonds and halogens act in the reverse manner and repel electrons. Therefore, it is unlikely that hypnotic activity is due to electrical behavior. The bulkiness of the auxiliary groupings may shield the cell from the metabolite and, in this manner, precludes access of metabolites and inhibits activity. The polar groups presumably show some degree of hydrogen bonding (Chap. 8) and become attached to the receptor. A balance between water and lipoid solubility of a molecule is necessary so that the molecule can reach the cell and still act on it. This balance between water and lipoid solubility governs the rapidity of onset of action. Likewise, the toxicity and cumulative effects of these hypnotics depend on the ability of the organism to attack the bulky part of the molecule by an oxidative or other biochemical mechanism. In certain of the barbiturates, thiopental for example, the side chains on carbon 5 are attacked

by oxidation or by hydrolysis. Drugs having branched chains, radicals, halogens or double bonds as substituents are the most reactive.

NON-BARBITUATE HYPNOTICS

Prior to the development of the barbiturates, the aliphatic hypnotics were the only suitable substances available in therapeutics. These, for reasons of lesser toxicity and greater therapeutic versatility, were supplanted by the barbiturates. There has been a trend in recent years to depart from the barbiturate structure and to seek hypnotics which are not related to them chemically. As a result of this attempt to depart from the configuration characteristic of the barbiturates, a number of compounds have been introduced which are structurally dissimilar, but pharmacologically similar. The structures of all of these, as is the case with other hypnotics, have an active hydrophilic group attached to an electrophilic center upon which appears an inert and bulky residue. One class of compounds is built around the piperidine nucleus (Table I.20). One of the better known and most important of the piperidine series is methyprylon, otherwise known as Noludar. Another, glutethimide, is derived from glutarimide. Another, Dolitron is derived from the thiazane nucleus. These are discussed in more detail later on.

Methyprylon (Noludar)

STRUCTURE

In methyprylon the piperidine structure has been converted into a dione.

TABLE I.20
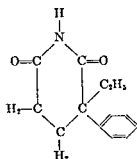
α Phenyl Ethyl Glutarimide
(Glutethimide, Doriden)
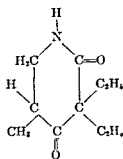
Methyprylon
(Noludar, Noctan)
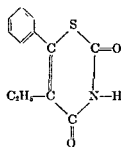
5 Ethyl 6 Phenyl
Metathiazine-2,4,-Dione
(Dolitrone, M.R.D. 125)
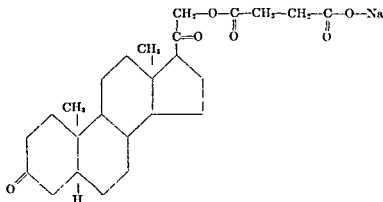
21-Hydroxy Pregnane-3,20,-Dione Hemisuccinate
(Sodium Hydroxydione, Viadril)

Two ketonic oxygen atoms are on the two and four position (Table I.20). The

$$-N-C=O$$

group acts as the polar group or hypnophore group. In addition a methyl group is present in position five. Two ethyl groups appear on position three instead of two hydrogen atoms. These two radicals confer the bulk necessary for inertness. Chemically this structure is known as 3, 3-diethyl 5-methyl, 2, 4 piperidine dione.

PROPERTIES

Methyprylon was introduced by Pellmont, Jurgen and Struder in 1955. The substance is a white crystalline powder which melts at 74–77°C. It has a bitter taste, is soluble in water, alcohol, benzine and chloroform. The compound possesses sedative and hypnotic properties similar to the intermediate and short acting barbiturates It is used primarily for sedation, is not analgesic or anesthetic and is, therefore, inadequate for surgical anesthesia. The drug is absorbed rapidly from the gastrointestinal tract. Peak plasma levels are attained one to two hours after oral administration. Approximately 3% of the drug is excreted into the urine unchanged. A small amount is excreted as a dehydrogenated derivative.

Glutethimide (Doriden)

STRUCTURE

Another departure from the barbiturates as hypnotics is the group derived from glutarimide, the imide of glutaric acid (Table I.20). This gives rise to a series of derivatives most important of which is glutethimide. (Table I.20). In this case the

$$\underset{O}{\overset{O}{\|}}\overset{O}{\underset{O}{\|}} -C-NH-C-$$
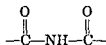
group acts as the polar group and confers hydrophilic properties to the structure. There is some resemblance between the glutarimide structure and the pyrimidine ring of the barbiturates. Glutarimide possesses an alpha and a beta carbon each of which bear two hydrogen atoms, both of which may be replaced by alkyl and other radicals (Table I.20). Substitutions on the alpha carbon yield hypnotics while substitutions on the beta carbons yield compounds of low narcotic potency or with central stimulating properties. This characteristic of conversion of a hypnotic to a stimulant by slight changes in molecular configuration is discussed in Chapter 24. Substitution of an ethyl and a phenyl group for both hydrogen atoms on the alpha carbon yields glutethimide (Doriden) which is a serviceable hypnotic. Glutethimide, therefore, is alpha phenyl ethyl glutarimide (Table I.20). It could also be called 3 ethyl, 3 phenyl, 2, 6 piperidine dione. Its structure, therefore, might be considered to be allied to that of methyprylon (Noludar). Substitution of a methyl and an ethyl group on the beta position yields bemegride (Megimide). This is a stimulant and a convulsant and is suitable as an analeptic.

PROPERTIES

Glutethimide was synthesized in 1952 under patents held by the Ciba Pharmaceutical Works. The compound was synthesized in 1952 by Tagmann and Sury and Hoffman. Glutethimide is a white powder which forms crystals from ether which melt at 84°C. The drug is insoluble in water but is soluble in organic solvents, particularly alcohol and chloro-

form. The compound forms a hydrate and a very water soluble hydrochloride which are not used medically. Glutethimide is a short acting central nervous system depressant which is administered orally as a hypnotic and a sedative. The drug is soluble in proplene glycol. Solutions of the drug in this solvent have been used intravenously. The potency of glutethimide as a depressant in laboratory animals is similar to that of phenobarbital.

METABOLISM AND DISTRIBUTION

Absorption by the oral route is rapid, possibly due to conversion of the compound to the soluble hydrochloride in the stomach. The compound at first is distributed uniformly in the watery tissues throughout the body. The drug tends to become concentrated in the fat, liver and other tissues several hours after ingestion. Glutethimide labelled with radioactive isotopes is retained in the gastrointestinal tract. Approximately 35% of the radioactivity still remains in the gastrointestinal tract 16 hours after ingestion. Presumably this is due to the fact that more than 60% of the drug and the end products of metabolities are excreted into the bile. The drug is re-absorbed as the bile passes into the intestine. The compound which becomes concentrated in the urine is not glutethimide but one of its metabolic products. Approximately 35% of the byproduct is excreted into the urine in the first 15 or 16 hours. No glutethimide as such is recoverable in the urine of the dog. Presumably the compound undergoes deethylation and the metabolite is excreted as alpha phenyl glutarimide. About 5% of this is a conjugated derivative of alpha phenyl glutarimide.

Dolitrone

STRUCTURE

Another departure from the classical barbiturate configuration is the drug known as Dolitrone. This is a cyclic compound developed commercially by the W. S. Merrell Company for use as an intravenous anesthetic. The drug was studied clinically by Lundy in 1956. The cyclic structure from which Dolitrone is derived is the thiazane nucleus which has incorporated in its molecule an atom of sulphur, one of nitrogen, and four of carbon (Table I.20). Thus, like the barbiturates, Dolitrone is a hexacyclic structure. Chemically Dolitrone is 5 ethyl, 6 phenyl meta thiazine-2, 4 dione. In other words, if the ring is numbered 1 to 6 beginning at the sulphur atom, a ketonic oxygen appears on position 2 and 4 (Table I.20). The compound possesses the characteristic hydrophilic and lipophilic groupings found in other hypnotics. One double bond is present between carbons 5 and 6. The bulky inert part of the molecule is the portion of the ring carrying the ethyl and phenyl groups (carbon 5 and 6).

PROPERTIES

The drug is a feeble acid which is almost totally insoluble in water. The compound dissolves in sodium hydroxide to form a soluble sodium salt, the aqueous solutions of which are highly alkaline. The pH of the aqueous solution ranges between 12 and 13.

The hypnotic and basal narcotic effects of Dolitrone are similar in most respects to those of thiopental. The drug fell into disfavor shortly after its introduction because of difficulties in forming stable, non-irritating solutions. Considerable venous irritation, local throm-

bophlebitis and slough were encountered. The drug penetrates the blood brain barrier as readily as does thiopental. Induction of anesthesia, therefore, is rapid. In view of the fact that the drug had little to offer over the thiobarbiturates available at the time, little enthusiasm was generated for its acceptance and few studies were done on its distribution and metabolism.

Steroid Hormones (Viadril)

STRUCTURE

Another group of derivatives which depress the nervous system are the steroid hormones. As early as 1941 Selye noted that the female sex hormones, particularly progesterone, were capable of producing both local and systemic anesthesia if injected in large doses in rats. This observation was pursued further and in 1955 Laubach and his associates, at the Pfizer Laboratories, introduced hydroxydione. Many other steroid derivatives possess depressant activity but most of those which appear to be serviceable possess many side actions. Selye noted that the anesthetic potency of steroids is related to the absence of double bonds and oxygen atoms on the steroid structure. Hydroxydione is a steroid derivative. The proprietary name in the U.S. is Viadril. The compound has also been known under the name of Presuren. Hydroxydione possesses the basic cyclopentenophenanthrene ring which forms the basis of the steroid hormones, the carcinogenic hydrocarbons, the bile acids, the sterols and so on (Table 1.20). Chemically hydroxydione is 21 hydroxy pregnane 3–20 dione sodium hemisuccinate (Table 1.20). It is chemically related to progesterone. The drug is prepared by the palladium reduction of desoxy-corticosterone. This intermediate product is then treated with succinic anhydride after which the sodium salt is formed.

PROPERTIES

The compound, therefore, is an acid which forms a sodium salt. The sodium salt is a lyophilized fluffy white powder which decomposes at 193°–203°C. The free acid melts at 195°–197°C. The free acid dissolved in chloroform has a dextro rotation of $+95°$ at 20°C. using a sodium light. The compound absorbs ultra violet light so that it may be estimated quantitatively on a fluorometer. The maximum absorption occurs at 280 mμ.

The sodium salt is soluble in water and in mildly alkaline buffer solution. Solutions have a soapy appearance. It is also soluble in acetone and chloroform. The pH of the 2% aqueous solution and the strength in which it is used varies, from 8.5 to 9.8.

DISTRIBUTION AND METABOLISM

The compound is devoid of hormonal properties. It acts primarily as a basal narcotic requiring supplementation with nitrous oxide or other form of analgesia or anesthesia. It has a latent period which ranges from 5 to 10 minutes following the injection of predetermined doses.

The compound is metabolized by the liver. Presumably it is conjugated by enzymatic action to pregnane 3,20 diol 20 one-21 hemisuccinate and pregnane 3,21 diol–20,1.

BIOCHEMICAL EFFECTS OF STEROIDS

Some steroid hormones directly affect the consumption of oxygen by brain in vitro. It has been demonstrated that there is a parallelism between anesthetic

action of steroids and their ability to inhibit oxidation of glucose in brain homogenates. The quantities of steroids used in these studies, however, were in excess of those involved in normal physiological function. Stilbesterol, which is a steroid hormone, differs in this regard, however, because it inhibits respiration of the brain in vitro more strongly than other steroids in comparable concentration, but has a relatively low anesthetic potency. Severe adrenal insufficiency is accompanied by slowing of the electrical discharges in the brain when studied by means of the electroencephalogram. The electroencephalographic pattern is restored to normal by the administration of cortisone or cortical hormones in the rat. Changes in the electroencephalographic frequencies occur after adrenalectomy and revert to normal after the addition of cortical hormones. Desoxycorticosterone, dehydroisoandrosterone and testosterone in amounts in excess of those found physiologically depress consumption of oxygen by slices of rat brain. The nature of the suppression is likely to be a reaction common to all oxidations, possibly one involving the flavoprotein of the electron transfer system. The action of hydroxydione is believed to be due to inhibition of the entrance of glucose into the tricarboxylic acid cycle.

TRANQUILIZERS

DEFINITION OF THE TERM

The term tranquilizer, unfortunately, has become widely accepted in medicine. The term is not a pharmacological one but is instead a psychological one which is used to designate a group of widely diversified drugs which are dissimilar not only in chemical structure but also in pharmacological activity. The term infers that such drugs cause depression of the nervous system. This is generally true, but not always the case, since both stimulants and depressants appear to be included in the classification. There is no specific area in the nervous system which is responsible solely for "tranquility." The term "tranquility" in itself is a nebulous one which conveys a meaning which may be interpreted in a variety of ways depending upon the individual hearing the term.

CLASSIFICATION

Of the two types of drugs included among the tranquilizers, the depressants and the stimulants, the anesthetist is interested primarily in the former. The depressant drugs may be classified as (a) non-selective and (b) selective. Among the non-selective are included the aliphatic hypnotics, the urea derivatives, the narcotics, and other pharmacologically allied compounds mentioned in the previous chapters. Those which act selectively appear to act on specific, localized areas in the brain or spinal cord. Among these are (1) the anti-convulsants, (2) drugs which act centrally to suppress histamine activity, such as Phenergan, (3) drugs which suppress activity within the spinal cord and produce varying degrees of muscle relaxation. They reduce "tension" by relaxing muscles by reducing the number of impulses coming over the internuncial neurons. Mephenesin and meprobamate are among this group. (4) Drugs which suppress central parasympathetic activity, such as benactyzine and Vistaril and (5) drugs which act as central sympathetic depressants. Among these are the phenothiazines and the alkaloids derived from Rauwolfia.

CHEMICAL TYPES

The more important selective depressants may be classified from a chemical standpoint into four major groups. (1) Compounds derived from phenothiazine. This includes a large series of similarly related structures (Table II.20). (2) Alkaloids derived from Rauwolfia. This includes Rauwoloid, Raudixin, Reserpine, Deserpidine, Recimamine and related

TABLE II 20

PHENOTHIAZINES

	R₁	R₃
Trimeprazine (Temaril)	—CH₂—CH—CH₂—N(CH₃)₂ CH₃	H
Promethazine (Phenergan)	—CH₂—CH₂—N(CH₃)₂ CH₃	H
Promazine (Sparine)	—CH₂—CH₂—CH₂—N(CH₃)₂	H
Chlorpromazine (Thorazine)	—CH₂—CH₂—CH₂—N(CH₃)₂	Cl
Trifluoropromazine (Vesprin)	—CH₂—CH₂—CH₂—N(CH₃)₂	CF₃
Mepazine (Pactal)	—CH₂ [ring]N—CH₃	H
Perchlorperazine (Compazine)	—CH₂—CH₂—CH₂—N [ring] N—CH₃	Cl
Trifluoroperazine (Stelazine)	—CH₂—CH₂—CH₂—N [ring] N—CH₃	CF₃
Thiopropazate (Dartal)	—CH₂—CH₂—CH₂—N [ring] N—CH₂—CH₂—O—C—CH₃ O	Cl
Perphenazine (Trilafon)	—CH₂—CH₂—CH₂—N [ring] N—CH₂—CH₂—OH	Cl
Thioridazine (Mellaril)	—CH₂—CH₂ [ring with N—CH₃]	—S—CH₃
Thioperazine (Vontil)	—CH₂—CH₂—CH₂—N [ring] N—CH₃	—S—N=(CH₃)₂ (with two O)
Pipamazine (Mornidine)	—CH₂—CH₂—CH₂—N [ring] C—NH₂ O	Cl

compounds. (3) Compounds derived from diphenylmethane and (4) Compounds derived from the substituted propanediols, glycodiols, and other hydroxylated compounds. These are prepared as esters of carbamic and other acids. There are, of course, others but these are the more important. Some anesthesiologists became enthusiastic about the non-selective depressants shortly after they were introduced. Actually they have limited usefulness in anesthesiology. The milder selective depressants have little to offer over the non-selective drugs for pre-anesthetic sedation. The Rauwolfia alkaloids and the phenothiazines are of interest to anesthesiologists because of their numerous varied responses, their side actions and their sustained effects.

PHENOTHIAZINES

Probably the most widely used compounds and those of the greatest interest to the anesthesiologist are the phenothiazine derivatives. They possess among a multitude of actions a selective inhibition of subcortical centers in the central nervous system, the reticular system, the thalamus and the autonomic centers. Phenothiazine itself has no particular action on the nervous system.

The phenothiazine structure possesses three rings (Table II.20). The center six-membered ring has a sulphur and a nitrogen atom. The two outer rings are benzene rings. On the basis of chemical structure the phenothiazine derivatives may be divided into groups according to the type of side chains which are substituted on the nitrogen atom (position 10) and on the hydrogen atom on position 2 of one of the benzene rings. These may be divided into groups as follows: (1) The chlorpromazine type. These are characterized by an aliphatic chain of three or more carbon atoms attached to the nitrogen atom. A halogen may appear on the position 2. In this group are promazine (Sparine), chlorpromazine, (Thorazine), trifluoropromazine (Vespirin), and promethazine (Phenergan). (2) The piperazine type. A piperazine ring is present in the aliphatic chain attached to the nitrogen atom. In this group are fluorophenazine (Stelazine), trifluoroperazine (Trilafon), perphenazine, thiopropazate (Dartal) and prochloropramazine (Compazine). (3) The piperidine group. A piperidine ring appears in the aliphatic side chain. In this group are mepazine (Pactal), and pipamazine.

Each of these compounds are qualitatively similar but quantitatively different in the intensity of their diverse actions. They differ in potency according to the side chain present. The least potent of this group is mepazine which does not contain a three carbon chain attached to the nitrogen atom. It has instead a methyl piperidine group with an intervening carbon. Promazine has a three carbon straight chain. It is less potent than chlorpromazine or trifluoropromazine. The chlorine endows to chlorpromazine twice the potency of the promazine which is devoid of it. The trifluoromethyl group confers upon the compound a potency of two to three times that of chlorine. Of the halogens only chlorine and fluorine appear to be suitable in increasing potency. The fluorine must appear as a trifluoromethyl group. Compounds having a piperazine nucleus in the side chain attached to the nitrogen are more potent than those having a simple aliphatic chain as is found in the chlorpromazine type. This increase in potency is due specifically to the addition of the piperazine ring to the

side chain. Halogenation of the piperazine compound is equally as effective in increasing potency as it is in the straight side chain derivatives. The trifluoro derivatives are at least double the potency of the chlorinated counterparts. A given phenothiazine, regardless of the type, has its potency increased with either of these halogens. The trifluoromethyl group in particular endows phenothiazine compounds with the maximum potency so far known.

The phenothiazines were first synthesized by Bernthsen in 1893. The sedative effects went unnoticed until 1945 when French workers began to study them. Promethazine was one of the first to be used. Charpantier resynthesized chlorpromazine in 1950.

Chlorpromazine

Chlorpromazine (Thorazine) is the prototype of a series of phenothiazine derivatives about which the numerous modifications revolve. Chemically it is 2, chloro 10, dimethylamino propyl phenothiazine. The substance is a base which is liquid and boils at 200°C. It forms a salt with hydrochloric acid. The salt is a greyish white powder soluble in water (1 gm. in 2.5 ml. H_2O). Aqueous solutions are acid in reaction having a pH of 5. Solutions turn brown on exposure to light and should be stored in light-proof containers. The powder is stable but decomposes at 179–180°C. It is soluble in alcohol and chloroform but insoluble in ether and benzine. The configuration is one which suggests both antihistamines and local anesthetics. However, both actions, if present, are feeble. The drug antagonizes epinephrine and norepinephrine both centrally and peripherally. Whether or not the action is competitive is not known. The drug potentiates the action of hypnotics and analgesics and inhibits the release of the adrenocorticotropic hormone from the pituitary. It sedates the chemoreceptor zones of the vomiting center acting competitively, presumably with the excitants upon the receptors in that area.

Chlorpromazine is eliminated as a sulphoxide. Up to 15% of a given dose appears in the urine. None is recovered unchanged.

MEPROBAMATE

STRUCTURE

Meprobamate is widely used as a tranquilizer for the control of anxiety. The compound is also known as Equanil, Miltown, Mebatin, Biobamate and by a host of other names. The compound is a derivative of 1, 3 propane diol (Table III.20). Carbon 2 carries a methyl and a propyl group. Carbons 1 and 3 carry hydroxyl groups which are esterified with carbamic acid. The compound, therefore, is a carbamate.

PROPERTIES

Meprobamate is a white crystalline substance which melts at 104–106°C. It possesses a characteristic bitter taste. It is soluble in water at 20°C. to form a 34% solution. At 37°C. it forms a 79% solution on a weight per weight basis. It easily forms supersaturated solutions with hot water. It is freely soluble in most organic solvents. Aqueous solutions are neutral. The substance is stable in dilute acids and alkalis and is not broken down by the gastric and intestinal ferments.

The drug produces tranquility by acting at specific areas in the nervous system. It bears a chemical relationship to mephenesin and like mephenesin suppresses polysynaptic neuronal activity in the spinal cord.

TABLE III.20
PROPANDIOLS
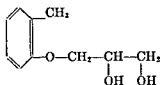
Mephanesin (Tolserol)
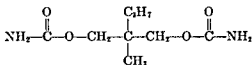
Meprobamate (Equanil, Miltown)
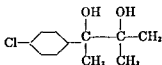
Phenagycodol (Ultran)

DIPHENYLMETHANE DERIVATIVES
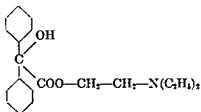
Benactyzine (Suavitil)
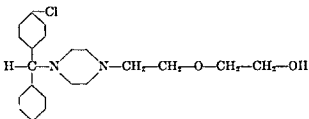
Hydroxyzine (Atarax, Vistaril)

DISTRIBUTION

Approximately 10% is excreted unchanged in the urine. A variable portion is conjugated probably with glucuronic acid and excreted into the urine. The remainder is metabolized but the exact fate is not known.

PHENAGLYCODOL

Phenaglycodol (Ultran) is in many respects similar in structure to meprobamate since it is also a diol (Table III.20). Chemically it is 1, 2 propane diol. A parachlorphenyl group appears on carbon 3. Therefore, its chemical name could be 2 parachlorphenyl, 3 methyl, 2, 3 butane diol. Like meprobamate it has a quieting effect and acts centrally to de-press polysynaptic pathways in the spinal and supraspinal levels.

AZACYLONOL

Among the derivatives of diphenyl methane is azacylonol. This compound is known as Frenquil. It is an isomer of piperodol which is a psychomotor stimulant.

Another tranquilizer, diphenyl methane derivative, is benactyzine, also known as Suavitil. Likewise it is a selective depressant. Its structure is shown in Table III.20. Hydroxyzine likewise is a central depressant. Here too it is a diphenyl methane derivative with a complex structure which in some ways resembles the antihistamines (Table III.20).

Local Anesthetics

DIFFERENCES BETWEEN LOCAL AND GENERAL ANESTHETICS

GENERAL ANESTHETICS are blood borne and, therefore, exert their effects on the central nervous system by being disseminated throughout the organism as a whole. Local anesthetics, on the other hand, act at a specific area. They must be applied directly at some easily accessible portion of the nervous system. The plasma level is, comparatively speaking, infinitesimal. As a rule, serious untoward responses develop should they gain access to the vascular system in significant quantities. Generally, they are applied to a peripheral nerve which is, in a sense, a bundle of axones. The axone transmits stimuli from a nerve cell to a receptor organ or to another neuron. Local anesthetics interrupt impulse transmission by causing temporary reversible changes in the chemical make-up of a neuron. They act anywhere in a neuron. However, the end result is the same irrespective of the point of application to a neuron, whether it be dendrite, cell body or axone—a blockade of impulse transmission.

PROPAGATION OF IMPULSES IN NERVE FIBRES

In order to understand how local anesthetics interrupt the propagation of impulses along a fibre and cause anesthesia it is necessary to interject at this point a description of the mechanism by which the transmission of a nerve impulse occurs. A membrane referred to as the *plasma membrane* delineates the cytoplasm of a nerve fibre from the surrounding extracellular fluid. This membrane, composed of lipoids and proteins, is believed to be several molecules thick. It is not histologically discernible. Normally a stimulus applied to a nerve fibre establishes an electrical current called an *action potential* in the plasma membrane in the area of stimulation. This action potential is propagated in succession to contiguous areas along a fibre to the point of termination. When the fibre is in the resting state the plasma membrane is permeable to certain ions, notably potassium and chloride, and impermeable to others, notably sodium, proteins and the ions of the amino acids. The protein ions are, as are those of sodium and potassium, positively charged since they are derived from the amino acids composing the nerve. As a result of this selective permeability a difference in ionic concentration develops on either side of the membrane. An ionic equilibrium for potassium and chloride is established according to Donnan's Law. In a resting fibre the concentration of potassium ions on the interior of the membrane is greater than at the exterior. The probable ratio is 5 inside to 2 outside. During

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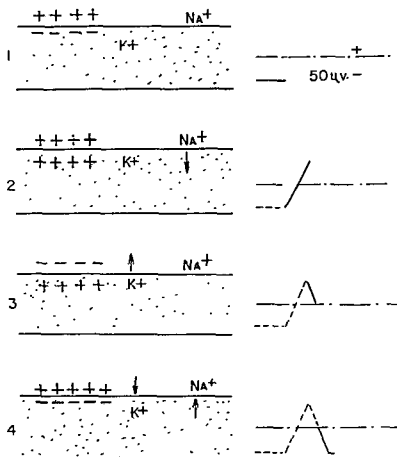
FIG. 1.21. Exchange of potassium and sodium ions and electrical activity in a nerve fibre.

(1) Resting fibre. Potassium ion predominates inside the membrane, sodium outside. The membrane potential is negative in the interior with reference to the exterior at 50 millivolts.

(2) Activity commences. The permeability is changed by the excitor substance to allow sodium ions inward (arrow). Potassium ion lags and the concentration remains unchanged for the moment. The polarity is reversed and the potential overshoots to 50 millivolts on the positive side.

(3) Potassium ion migrates outward. The potential becomes zero. The polarity is the same inside the membrane as out for a moment after which it becomes positive.

(4) Returning to the resting state. The sodium ions are extruded outward by the "sodium pump." Potassium ions migrate inward. The potential reverts to the resting level.

The dotted lines indicate the sequential changes in potential. The full lines indicate the potential at the moment. The shift of chloride and other anions is not shown, but occurs concomitantly with shift of anions.

inactivity a difference in electrical potential develops between the exterior and the interior of the membrane as the result of this asymmetric ionic distribution. The polarity of the interior of the membrane is negative with reference to the exterior. Sodium ions are extruded through the membrane during the resting phase from the interior where the concentration is minimal to the exterior of the fibre where the concentration is maximal by a mechanism referred to as the "sodium pump." Exactly how the "pump" operates is not fully understood. Possibly the enzymatic breakdown of lactic and pyruvic acids provides the energy necessary to operate the "sodium pump" which is moving ions against a

gradient. This has not been definitely established, however. A potential difference in the neighborhood of 100 millivolts develops; negative on the inside and positive on the outside of the membrane. This potential difference is referred to as the *demarcation potential*. When a stimulus initiates the excitation wave the permeability of the plasma membrane is altered in the area of excitation. The sodium ions are then able to migrate inward. This is accomplished by liberation of a transmitter substance in the nerve fibre. The composition was not definitely known until recently. It has now been established that this substance is acetyl choline. The liberation of the transmitter substance is initiated at the point of stimulus. The liberation continues in each successive area as the excitation wave sweeps along the fibre from one contiguous zone to another. The process is repeated in a relay-like manner as the impulse is propagated along the axone. Not only do sodium ions migrate inward but potassium ions are simultaneously passing outward to the exterior. The migration of sodium ions inward precedes the migration of potassium ions outward. The balance is disturbed by this lag so that the membrane, thus, becomes depolarized. In other words the potential is rapidly decreased to zero after which the exterior becomes negatively charged with reference to the interior. The polarity is thus reversed. This reversal is only of momentary duration since the potential swings swiftly to the opposite charge on the interior. This is opposite to the state of affairs noted during the resting phase. As soon as sufficient potassium ions migrate outward the membrane potential on the interior equals that of the exterior and is, therefore, isoelectric once again

(zero value). The fibre is then in the refractory period and inexitable. This period of electrical neutrality is of discernible duration. The "sodium pump" then begins to operate and the sodium ions are then extruded to the exterior from within the fibre. Potassium ions then return inward, presumably by a "pump" mechanism also, and the membrane potential is restored to its normal or resting state with the polarity of the interior negative and that of the exterior positive. Simultaneously with the movement of cations there is a migration of appropriate anions. These changes occur rapidly in a matter of milliseconds each time a nerve impulse is transmitted along the fibre.

INTERRUPTION OF CONDUCTION

It is obvious that agents which interfere with the passage of ions through the plasma membrane or which alter the membrane potential prevent the passage of impulses through the area so altered. Thus, a blockade is accomplished in one of two ways, (1) by stabilizing the membrane so that the forementioned changes in permeability cannot take place or (2) by causing depolarization of the membrane. Local anesthetics act in the former manner and stabilize the membrane thereby preventing the changes in permeability necessary for propagation of an impulse from zone to zone. The demarcation potential normally present in a nerve remains unchanged. Solutions of ionizable potassium or calcium salts, likewise, cause a blockade. However they do so by the latter mechanism. They cause depolarization and do not act by stabilization of the membrane. The demarcation potential is nullified by these ions so that the changes in polarity necessary for conducting the impulse do not

occur. The situation in many ways parallels the depolarizating action of decamethonium at the myoneural junction (Chap. 23). The action of local anesthetics, in some ways, may be likened to the behavior of d-tubocurarine which, at the myoneural junction, produces a block by inhibiting the changes in polarization normally caused by acetyl choline.

LIPOPHILIC-HYDROPHILIC PROPERTIES OF LOCAL ANESTHETICS

Local anesthetics are both water and lipoid soluble. This lipoid solubility is necessary for their passage into the neural fibre since it is rich in lipoids. The water solubility is necessary for their *carriage to the fibre by lymph, which is* largely water. A balance between these two solubilities is necessary for optimal activity. An excessively high lipoid solubility and correspondingly poor water solubility renders a compound ineffective because the quantity transported to the fibre is inadequate. The reverse situation, a high water solubility and a low lipoid solubility, favors adequate transport but poor penetration into the fibre. The molecules of all effective local anesthetics have both lipophilic and hydrophilic groupings which confers this necessary, mixed solubility. Generally, the hydrophilic portion of the molecule is an *amino* group. Less often it is a *hydroxyl* group. The lipophilic portion consists of a *hydrocarbon* residue of some sort. Actually, the nerve fibre is a lipoid rich, metallo-protein unit surrounded by an aqueous phase. The hydrocarbon residue becomes oriented into the lipoid phase and the amino or hydroxyl group into the metallo-protein phase in the fibre and surrounding aqueous medium.

CHEMICAL NATURE OF LOCAL ANESTHETICS

Numerous substances manifest local anesthetic activity. The ability to block neural transmission is not necessarily an attribute of a *single type of molecular* configuration. Many compounds with diversified molecular configurations are capable of causing a blockade. In many cases the local anesthetic effect is one of several actions possessed by a drug and not necessarily the principal action. This overlapping of action is discussed further on.

Hundreds of compounds have been prepared and studied for local anesthetic activity. Many have been discarded because they are locally irritating or toxic systemically. In classifying local anesthetics presently in clinical use, two types of compounds appear to predominate—*hydroxy compounds* and *amines.* Derivatives in the hydroxy group are used mostly for surface anesthesia. The amines are the more important type. The majority of local anesthetics in clinical use fall into this group. Drugs which manifest local anesthetic activity which do not fit into either of these categories are available but are not clinically important.

HYDROXY COMPOUNDS

The hydroxy compounds are alicyclic or aromatic alcohols. As a rule, aliphatic hydroxy compounds are ineffective as local anesthetics unless an aromatic nucleus forms part of the structure. The hydroxyl group invariably is attached to a hydrocarbon nucleus of some type. The *hydroxyl group is hydrophilic* and orients itself into the aqueous phase; the *hydrocarbon is lipophilic,* and orients itself into the lipoid phase of the neural preparation.

The simplest aromatic alcohol is hydroxybenzine or *phenol*. This has been used in dilute solutions on the unbroken skin for the alleviation of pruritus. It is highly irritating and caustic. Related to phenol are the aromatic methyl hydroxy benzines or *cresols*. These have properties similar to phenol but are less important because they are more toxic. Interposing a carbon atom between the aromatic nucleus and the hydroxyl group reduces its local toxicity and enhances its local anesthetic effect.

The substitution of a phenyl group for one of the hydrogen atoms in methyl alcohol results in phenyl methanol or *benzyl alcohol*,

$$\langle\!\!\!\!\bigcirc\!\!\!\!\rangle\!-\!CH_2OH.$$
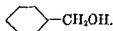
Benzyl alcohol is suitable for surface anesthesia in concentrations up to 10%. It is locally irritating and may cause neurolysis when injected perineurally. A hydroxyl group in the ortho position converts benzyl alcohol to *saligenin*,

$$\langle\!\!\!\!\bigcirc\!\!\!\!\rangle\!-\!OH\,.$$
$$CH_2\!-\!OH$$

Saligenin possesses a topical anesthetic action comparable to benzyl alcohol. It is not suitable for infiltration because it, too, causes local tissue damage. A bromine atom introduced in the meta position with reference to the methanol group on the aromatic nucleus converts saligenin to *bromsalizol*,

$$Br\!\!-\!\!\langle\!\!\!\!\bigcirc\!\!\!\!\rangle\!-\!OH.$$
$$-\!CH_2OH$$
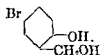
Bromsalizol is used for topical anesthesia (aqueous solutions) and as a neurolytic agent by direct injection (oily solutions). It also acts as an antispasmodic when taken orally.

Cinnamic alcohol,

$$\langle\!\!\!\!\bigcirc\!\!\!\!\rangle\!-\!CH\!=\!\!=\!CHOH$$
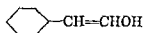
and phenyl ethyl alcohol,

$$\langle\!\!\!\!\bigcirc\!\!\!\!\rangle\!-\!CH_2CH_2OH.$$
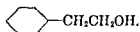
also produce topical anesthetic properties. Both compounds have similar alcohols. Secondary and tertiary alcohols, such as diphenyl carbinol,

$$H\!-\!C\!-\!OH$$
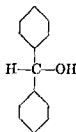
and dibenzyl phenyl carbinol,
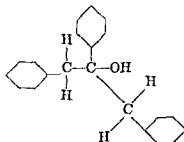
are weaker and less effective topical anesthetics than primary. They are seldom used in present day practice. Certain monohydric, cyclic alcohols, as for example, cyclohexanol and menthol, possess topical anesthetic action also. Certain dihydric alcohols (diols) manifest a feeble local anesthetic activity. *Mephenesin*, a propanediol, is an example of such a derivative.

Most hydroxy compounds are locally irritating when injected into the tissues and are, therefore, used chiefly for surface anesthesia. They tend to be neu-

rolytic and caustic, particularly if used to excess or if they are injected into the tissues. They also appear to be devoid of the convulsive manifestations which characterize the amines. Their mode of action in the nerve fibre is presumed to be different than that of the amines. The names of the hydroxy compounds usually end with the suffix "ol."

NITROGEN CONTAINING DERIVATIVES

The nitrogen containing group is the larger and more important and includes the majority of the clinically useful compounds. The configuration most consistently associated with local anesthetic activity is one composed of an aliphatic chain of two or more carbon atoms one end of which carries a hydrocarbon nucleus usually of the aromatic or alicyclic type:

$$\left\langle\right\rangle\!-\!CH_2\!-\!(CH_2)_n\!-\!N\!\overset{R_1}{\underset{R_2}{}}$$
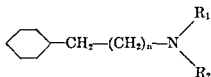
The nitrogen atom, usually in the form of a secondary or tertiary amino group, *is on the other end of the chain. Thus,* an aliphatic chain, sometimes referred to as the *pivot,* separates a *hydrophilic nitrogen atom* from a *lipophilic hydrocarbon residue.* The hydrocarbon nucleus is derived from organic carboxy acids and is linked to the aliphatic pivot by esterification or by an amide linkage, as a rule. Less often an ether type linkage binds the two. The majorty of injectable local anesthetics are esters of aromatic *acids and amino alcohols. Dibucaine* (Nupercaine) and lidocaine (Xylocaine) are two important exceptions. In these, the amide type of linkage unites the hydrocarbon to the pivot. In both lidocaine and dibucaine the pivot replaces

one of the hydrogen atoms of the amide of the acid portion of the molecule.

Nitrogen containing local anesthetics conforming to the forementioned type of general configuration are named with the suffix "caine." Generally, these compounds manifest qualitatively similar pharmacological properties. Systemically they cause an intense stimulation of the nervous system which is followed by depression. They may also induce severe cardiovascular manifestations characterized by depression of cardiac tissues. Substances with local anesthetic activity which do not possess this general chemical configuration do not manifest these systemic effects.

Not all compounds which conform to the forementioned general structure of hydrocarbon residue, pivot and amino group manifest local anesthetic activity, however. Compounds which would appear from their structure to be anesthetically active are not while others which are active do not conform to the generalization. Atropine, for example, meets the general specifications of a local anesthetic but possesses only slight local anesthetic activity. Certain narcotics, as for example, dionine (a phenanthrene derivative), the phenthiazine derivatives, and various anti-histaminics manifest varying degrees of local anesthetic activity but do not conform to this generalization. The barbiturates, if applied perineurally, produce a blockade. They, likewise, do not conform to the configuration.

OVERLAPPING OF PHARMACOLOGICAL ACTIONS

As is the case with many other compounds local anesthetics manifest an overlapping of action and have pharmacologic responses possessed by other drugs. Procaine, for example, possesses

a varying degree of anti-histaminic activity and some anti-cholinergic activity in addition to local anesthetic activity. Its outstanding attribute, however, is its local anesthetic activity. Atropine possesses a strong anti-cholinergic activity while also manifesting a feeble local anesthetic and anti-histaminic activity. Its use is primarily as an anti-cholinergic since this is its outstanding characteristic. Tripelennamine (Pyribenzamine) is a potent anti-histaminic but a feeble and irritating local anesthetic. It also possesses some degree of anti-cholinergic activity. Ephedrine is an amine manifesting some local anesthetic effect. However, its chief attribute is its sympathomimetic activity.

ATTRIBUTES COMMON TO AMINO ESTERS AND AMIDES

A closer examination of the structure of a typical member of the ester type compound reveals two striking points of significance. (1) The nitrogen atom is invariably on the terminal carbon of the pivot. The nitrogen forms a tertiary or secondary amine, rarely a primary amine. The amino group is of the alkamino (methyl, ethyl, etc.) type. However, it is not necessary for the nitrogen grouping to be of the alkamino type since it may be enclosed in a ring as it is, for example, in the piperidino group:

(2) The acid is invariably a cyclic one and in most cases an aromatic derivative. Local anesthetics derived from aliphatic carboxy acids have been prepared but are not clinically useful. The majority are derivatives of benzoic or some substituted benzoic acid.

CLASSIFICATION OF ESTERS AND AMIDES

Inasmuch as the amino esters and the amides comprise by far the largest and the most important group of local anesthetics, these will be discussed in detail. This group is large and diverse since many different alcohols and acids enter into the ester formation. These derivatives are best subdivided into classes according to the type of acid used to form the ester or amide.

BENZOATES

The simplest of the aromatic acids, benzoic acid, forms the basis of a number of important compounds (Table I.21). The first synthetic local anesthetics were benzoates of aliphatic amino alcohols. Stovaine, an early success (Fourneau, 1904), is an ester of dimethylamino tertiary amyl alcohol. The dimethylamino group replaces a hydrogen atom of the methyl group of the alcohol (Table I.21). A second basic dimethyl amino replacing a hydrogen atom on the methyl group of amyl alcohol converts stovaine to *alypin*. Both of these are aliphatic amino alcohols which have fallen into disuse.

Cocaine, likewise, is a benzoate. It is the benzoic acid ester of methyl ecgonine. The complex alcohol, methyl ecgonine, is derived by the fusion of two heterocyclic structures, one of which contains four carbon atoms and the other five. The nitrogen is common to both rings. In addition to the hydroxyl group a carboxyl group is present on ecgonine, so that it has the properties of both an alcohol and an acid. The carboxyl group is esterified with methyl alcohol (Table I.21). Failure to do so nullifies its anesthetic activity. Cocaine is a naturally occurring product. Attempts to simulate the structure of cocaine to produce less

TABLE I.21

BENZOIC ACID DERIVATIVES
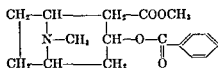
Cocaine
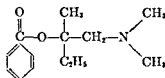
Stovaine
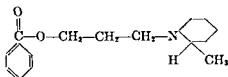
Piperocaine (Metycaine)
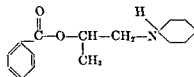
Hexylcaine (Cyclaine)

Kincaine
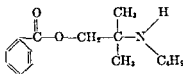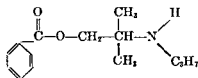
Meprylcaine (Oracaine)
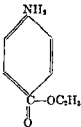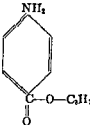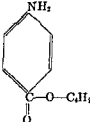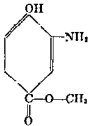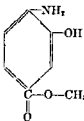
toxic compounds have yielded tropocaine and psicaine (Eucaine "A" and Eucaine "B"). In these the alcoholic portion of the molecule has the same complexity as ecgonine. Attempts have been made to simplify ecgonine by decreasing the carbon content by removing the four carbon ring. This has led to the study of a series of derivatives of *piperidine*. The most prominent of these are piperocaine (Metycaine) and cyclaine (Hexylcaine). Piperocaine is a benzoate of propanol in which a methyl piperidinyl group is substituted on the carbon (Table I.21). In piperocaine and cocaine the amino nitrogen is contained in a heterocyclic structure instead of being an aliphatic amino derivative. In hexylcaine a cyclohexenyl group replaces a hydrogen in the amino group of amino propanol which is used for esterification.

AMINOBENZOATES

By far the most numerous and extensively used local anesthetics are the esters prepared from aminobenzoic acid.

Aminobenzoic acid may have one of three configurations—the ortho (2), meta (3) and para (4). All three have been esterified with various amino alcohols to yield useful local anesthetics. Of the three series of aminobenzoates the para-aminobenzoates are the most satisfactory and widely used. Two series of para-aminobenzoates are known: (1) the soluble and (2) the insoluble. Esterification of para-aminobenzoic acid with simple aliphatic alcohols yields poorly soluble compounds with a feeble local anesthetic action and low toxicity. The ethyl ester, commonly known as *anesthesin* (benzocaine), is non-injectable but satisfactory for topical anesthesia. The propyl ester (*propaesin*) and the butyl ester (*butesin*) are similar to anesthesin. Butesin may be esterified with picric acid to form the well known *butesin picrate*, used for surface anesthesia. The methyl ester is without effect. However, a hydroxyl group placed in the ortho position with reference to the amino group converts it to *orthoform* which is, likewise, feeble

TABLE II.21
Insoluble Esters of Amino Benzoic Acid

Para Amino Benzoic Acid
(1, Carboxy, 4 Amino
Benzene)

Meta Aminobenzoic Acid
(1, Carboxy 3 Amino
Benzene)

Ortho Aminobenzoic Acid
(1, Carboxy 2, Amino
Benzene)

Ethyl Para Amino
Benzoate (Benzocaine)

Propyl Para Amino
Benzoate (Propaesin)

Butyl Para Amino
Benzoate (Butesin)

Orthoform (New)

Orthoform (Old)

and only used for topical anesthesia (Table II.21). An *orthoform "new"* has also been prepared. The amino group is in the ortho and the hydroxyl in the para position in this compound. The relative insolubility of these simple esters accounts for the low toxicity of this series and limits their usefulness except for topical anesthesia. The nitrogen atom in all of these is on the (aromatic) acid part of the molecule. All these derivatives are feebly basic.

SOLUBLE PARA-AMINOBENZOATES

The second or soluble group of esters of para-aminobenzoic acid is also formed

from aliphatic alcohols. In these the amino groups appear on one carbon of the alcohol also, usually the terminal carbon. Diethylamino ethanol esterified with para-aminobenzoic acid yields *procaine*. This is the same as placing a diethylamino group on anesthesin. The modification in structure increases both solubility and potency many, many times. Procaine forms a procaine amide (Pronestyl) which has low anesthetic potency but exerts a beneficial effect in cases of cardiac irritability.

Two nitrogen atoms are present on these aminobenzoate molecules, one on the acid and one on the alcohol part of

the molecule. By varying the carbon content of the alcohols and the alkamino radicals, branching the chain, and using various substituents to replace the hydrogen atoms on either amino groups, a series of useful anesthetics may be prepared, among which are tetracaine (Pontocaine), butethamine (Monocaine), larocaine, amylcaine and tutocaine. The structures of these are represented in Table III.21.

TABLE III.21

PARA AMINO BENZOIC ACID SERIES
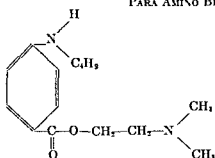
Tetracaine (Pontocaine)
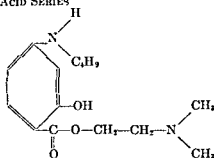
2 Hydroxy Tetracaine (Rhenocaine)
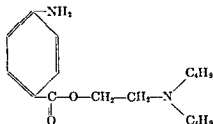
Butacaine (Butyn)
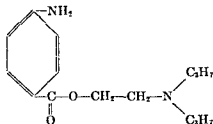
Isocaine
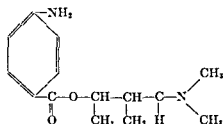
Tutocaine
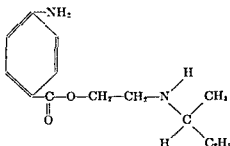
Butethamine (Monocaine)
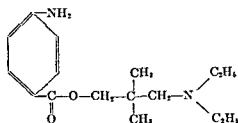
Larocaine
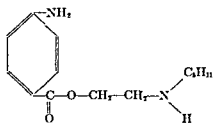
Amylcaine (Amylsine, Naepaine)

ORTHO-AMINOBENZOATES

The amino group appears in the ortho position in *peridocaine* (Lucaine) (Table V.21). The carboxyl group is esterified with piperidine propanol. This modification in structure results in a compound of lesser potency and solubility than procaine. Metabutethamine (Unicaine) has an amino group on the meta position instead of the para position. The acid is

TABLE IV.21
PROCAINE SERIES
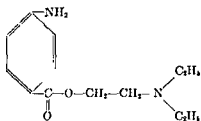
Procaine
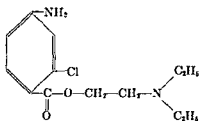
2 Chlor Procaine
(Nesacaine, Versacaine)
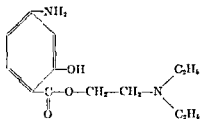
2 Hydroxyprocaine
(Oxyprocaine)
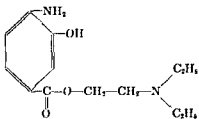
Metahydroxy Procaine
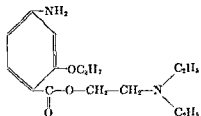
Propoxycaine
(Ravocaine, Pravocaine Blockaine)
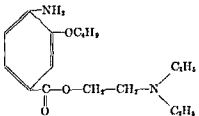
Metabutoxy Procaine
(Dorsacaine, Benoxinate)
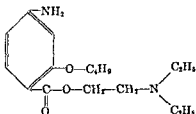
2 Butoxyprocaine
(Sympocaine)

TABLE V.21
MISCELLANEOUS ACIDS—SERIES

Ortho Amino Benzoates   *Meta Amino Benzoate*
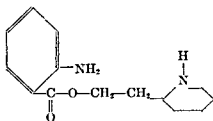
Piperidy Propanol Ester
(Piridocaine, Lucaine)
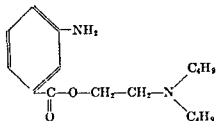
Metabutethamine
(Unacaine)
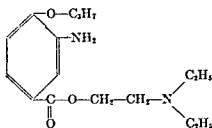
Proparacaine (Opthaine)
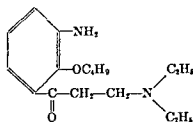
Metabutoxycaine (Primacaine)

Paraethoxybenzoates   *Cinnamates*
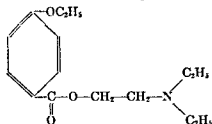
Maxicaine (Intracaine)
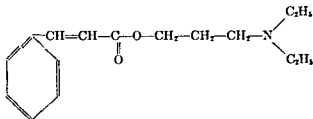
Apothesine

Carbamates
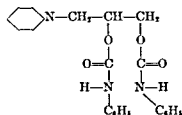
Diothane (Diperodon)
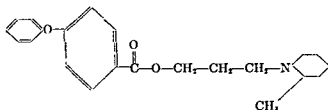
Cyclomethycaine (Surfacaine)

esterified with isobutyl amino ethyl alcohol.

ALKOXY BENZOATES

The alkoxy or ether linkage may be a substituent on the benzene ring. A series of para-ethoxy derivatives has been prepared most important of which is *maxicaine* (Intracaine). The carboxyl group is esterified with para-amino di-

ethylamino ethanol as is the case with procaine. The structure, therefore, is similar to procaine with the exception that an ethoxy group replaces the amino group in the para (4) position.

ALKOXY-AMINOBENZOATES

Combinations of both the amino and alkoxy group (ether linkage) on the benzene ring have been used to form procaine derivatives. *Benoxinate* (butoxyprocaine) has a butoxy group in the meta (3) position with reference to the carboxyl group. *Propoxycaine* has a propoxy group in position 2 with reference to the carboxyl group in procaine. *Primacaine* has a butoxy group in the meta (3) position of meta-aminobenzoate.

HYDROXY-AMINOBENZOATES

The hydroxyl group is substituted as a side chain on the benzine of the procaine molecule (Table IV.21). *Hydroxyprocaine* (Oxyprocaine) has the OH on position 2 (ortho) with reference to the carboxyl group. It is similar to procaine in properties. The hydroxyl group may be on position 3 (meta) in which case it is called *meta-hydroxyprocaine*. It also is similar to procaine in activity.

CHLORO-AMINOBENZOATES

Chloro derivatives of procaine, likewise, have been prepared (Table IV.21). Best known of these is a *2 chloroprocaine* (Nesacaine), which is similar to procaine in potency but less toxic and more easily hydrolyzed.

SUBSTITUTION INTO THE AMINO GROUP

Shortening the ethyl groups on the amino groups to methyl groups and replacing one of the hydrogen atoms of the para-amino group by a butyl radical converts procaine to *tetracaine* (Ponto-

caine, Amethocaine) (Table III.21). The potency and toxicity are both increased tenfold by this change. A hydroxyl group in the 2 (ortho) position with reference to the carboxyl group of tetracaine forms *hydroxytetracaine* (Rhenocaine).

CINNAMATES

An ethenyl group in the para position converts benzoic acid to cinnamic acid. Cinnamic acid has been used to form a series of local anesthetics, the most important of which is *apothesine*. The structure of apothesine, the cinnamate of diethylamino propanol, is shown in Table V.21.

PHENYL CARBAMATES

Phenyl carbamic acid forms a number of esters which possess anesthetic activity. *Diothane* is the most important of this type. Diothane is an ester of 1,2-dihydroxypropane. A piperidino group appears on the terminal nonhydroxylated carbon. Each hydroxyl group is esterified with a molecule of phenyl carbamic acid. The phenyl portion of the acid is considered the aromatic residue which confers the lipophilic qualities to the molecule; the piperidino group bears the tertiary amino nitrogen and confers hydrophilic properties. Esters less important than the aforementioned have been prepared but are rarely used clinically.

MISCELLANEOUS ESTERS

Esters of *fluoric acid* and various aliphatic alcohols possess local anesthetic activity but their use has been merely experimental. Ethyl morpholine derivatives of alcohol esterified with benzoic acid also possess local anesthetic activity. The series of drugs prepared by esterifying the alkaloid, cystisine, with organic acids yield drugs with anesthetic activity

but they are of no clinical importance. Naphthoic acid,
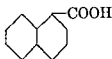
and amino naphthoic,
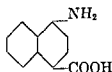
likewise, forms esters which possess local anesthetic activity. Bonacaine is the 2 hydroxy 2 naphthoate ester of diethyl amino propanol.

Substances which manifest pressor activity have been joined to amino-benzoic acid derivatives in the hope of obtaining drugs possessing combined pressor and anesthetic effects. These have met with little success. Acids in which sulphur replaces the oxygen atoms of the carboxyl group have been used to prepare esters of amino ethanol and other alcohols. These substances were found toxic and irritating.

AMIDES

The important non-ester derivatives are amides or analides. As is the case with the esters they, too, are derived from some acid which has the hydroxyl of the carboxyl group replaced by an amino group. A series of local anesthetic drugs has been prepared from quinoline. Of these, *dibucaine* (percaine, Nupercaine) is clinically important. Quinoline consists of a pyridine fused with a benzene ring. A carboxyl group on the pyridine nucleus converts it to cinchoninic acid. Instead of an ester, an amide is formed from the acid and a hydrogen of the amide group is replaced by ethylene diethyl amine. In addition a butyl-oxy group appears on the alpha position of the pyridine nucleus (Table VI.21).

Lidocaine (Xylocaine, Lignocaine) likewise is an amide. It may be looked upon as diethyl amino acetamide with one hydrogen of the amide grouping replaced by a 2, 6 dimethyl benzene. It also may be considered as 2, 6 dimethyl analine, with one of the amino hydrogens replaced by a diethyl amino acetyl group. Mepivacaine (Carbocaine) also is an amide allied to lidocaine. These are represented in Table VI.21:

MISCELLANEOUS

Numerous compounds are known which do not fit into the classification of hydroxy compounds, amides or esters which have local anesthetic properties. *Quinine* may produce prolonged local anesthesia. Chemically, quinine is a *cupreine*. A hydroxyl group is present as a side chain on a heterocyclic nucleus. It also possesses two nitrogen atoms which confer basicity to the compound. Eucupin, which is derived from quinine, also produces prolonged anesthesia, but possesses less local toxicity. The vinyl group of quinine is hydrogenated to remove the unsaturation and the methyl ether on the quinoline portion of the structure is converted to an isoamyl ether. The resulting *isoamyl hydrocupreine or eucupin* is less toxic than quinine and causes destruction of tissues. These derivatives are actually complex heterocyclic alcohols with substituted side chains. *Dimethoisoquine* (Quotane) is a derivative of isoquinoline but is neither an amide or an ester. A dimethyl amino ethyl group is linked to the nitrogen containing portion of the ring by an ester (oxy) linkage and a butyl group as in position 3. The drug is useful for surface anesthesia only. It is not a convulsant.

Certain phenyl ketones have been

TABLE VI.21

Amides and Amidines and Other Non Esters
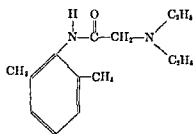
Lidocaine (Xylocaine)
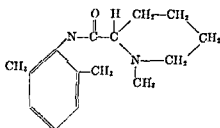
Mepivacaine (Carbocaine)
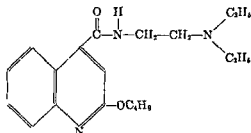
Dibucaine (Nupercaine, Percaine)
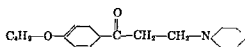
Dyclonine
(Dyclone, Falicain)
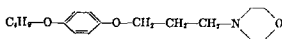
Pramoxine (Tronothane)
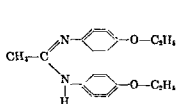
Ethenyl Diethoxy Diphenyl Amidine
(Holocaine, Phenacaine)
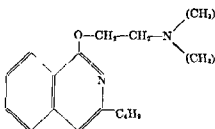
Dimethisoquin
(Quotane)

studied for their anesthetic potency. Among these is dyclonine (Dyclone) which is a 4 propoxyphenyl piperidino ethyl ketone. Though not an ester or an amide this derivative in most respects follows the general grouping of amino group, pivot and hydrocarbon residue. However, it is not a convulsant. Amidone, a narcotic, possesses a local anesthetic effect comparable to cocaine topically. Meperidine likewise has some local anesthetic action. Both are irritating to the cornea of animals and skin of man. The antihistamines are derivatives of phenylene diamine. They too do not

follow the general configuration of the ester and amide type compounds. They are not convulsant.

Parethoxy analine,

$$CH_3-O\bigcirc\!\!\!\!\!\bigcirc NH_2,$$
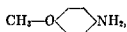
forms the basis of analgesic and anesthetic drugs. From it, the well known phenacaine (Holocaine) (Tauber 1897) has been prepared. Chemically it is N,N' di paraethoxy) phenyl acetamidine (Table VI.21). This is a strongly basic compound used for topical anesthesia. It is not suitable for injection.

RELATIONSHIP OF CHEMICAL STRUCTURE TO PHARMACOLOGIC ACTIVITY

A number of interesting relationships exist between the chemical structure and pharmacologic activity of the amino esters and amides. There are some compounds in which the nitrogen atom is incorporated in the heterocyclic nucleus. It still acts as a tertiary amine when arranged in this manner. Such an arrangement is found in cocaine, pipero-caine, diothane and many other derivatives. Conversion of an amino group in a potent local anesthetic to a quaternary base nullifies anesthetic activity. The aromatic nucleus is the most common hydrocarbon nucleus encountered in the clinically useful drugs. The aromatic nucleus is most often a single benzene ring which is either a plain phenyl radical or has side chains at various positions. However, the double benzene ring (naphthoic) nucleus may be present. Compounds with the double benzene ring tend to be less soluble. The hydrocarbon nucleus may also be derived from quinoline as it is in dibucaine. This is a double cyclic structure which is a fusion of an aromatic nucleus and pyridine.

Introducing an additional amino group in the molecule by placing it on the aromatic ring usually increases local anesthetic activity. This is a notable characteristic of the aminobenzoates. The position the amino group occupies in the ring influences potency. Compounds in which the amino group is in the para position with reference to attachment to the aliphatic side chain are more potent than those in which the attachment is in the meta or ortho position. Procaine, for example, derived from para-aminobenzoic acid is more potent than period-caine (Lucaine), which is similar in

structure but is derived from ortho-aminobenzoic acid. Substitution into the amino group on the ring also increases potency. Tetracaine, for example, has a butyl radical replacing one hydrogen atom of the amino group on the aromatic nucleus to form a secondary amine. In addition, the ethyl radicals on the alcohol portion of the molecule are shortened to methyl groups. The potency is increased 10 times by this alteration in molecular configuration. The alkoxy group entering the aromatic structure as a side chain increases potency, as for example, in oxyprocaine. As the length of the ether side chain increases both anesthetic activity and toxicity increase. The increase in toxicity, however, does not necessarily parallel the increase in anesthetic potency.

Simple esters of the aromatic series are relatively insoluble. Conversion to amines increases the solubility. The classic example is the conversion of ethyl para-aminobenzoate (benzocaine) to procaine, a diethyl amino compound. The amino group confers basic properties to the compound. Basicity is increased as well as solubility and potency. Increasing the length of the ester group (the pivot or isoteric group) decreases the basicity of the compound. The free base, therefore, is liberated at lower pH. Likewise the potency and toxicity of the compound are increased as carbon atoms are added. Lengthening the alkyl radicals on the amino nitrogen likewise decreases the basicity and increases potency and toxicity.

GENERAL CHEMICAL PROPERTIES OF LOCAL ANESTHETICS

With the exception of cocaine and other alkaloids extracted from coca

leaves local anesthetics are synthetic substances. Even though they are synthetic they possess the general chemical properties of alkaloids. All local anesthetics, as has been mentioned, are bases by virtue of the amino nitrogen groups in the molecule. They are, thus, able to form salts with acids. Aqueous solutions of the free base are alkaline. The basicity of the compound varies with the molecular configuration and degree of ionization. The pH range in most cases is between 7–8. Compounds having two amino nitrogen atoms, as for example, procaine, are, as a rule, more alkaline than those with one. Free bases are poorly soluble in water. The importance of the base in causing the physiologic alteration in the nerve is described later on. Alkalies (the hydroxides) and the alkaline salts (sodium bicarbonate) precipitate the free base from aqueous solutions of salts. The extent to which the base is liberated depends upon the alkalinity of the solution. The bases are viscid liquids or amorphous solids which, though sparingly soluble in water, easily dissolve in lipoids, oils, greases and various organic solvents. Suspensions of the bases are sometimes used for topical anesthesia. A suspension of cocaine base in water (cocaine milk, cocaine mud) is used for topical anesthesia. The rationale for its use is described later on. The base is used for preparation of ointments and oily solutions customarily employed for prolonged anesthesia. Most salts of local anesthetics are sparingly soluble or insoluble in lipoids and organic solvents.

Most local anesthetics are dispensed in the form of the salt. The formation of salts from the base and acid is similar to the union of ammonia with an acid or the neutralization of ammonium hydroxide by an acid:

$$NH_3 + HCl \rightarrow NH_4Cl$$
$$RNH_2 + HCl \rightarrow RNH_3 \cdot Cl$$
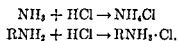
Salts of local anesthetics are crystalline substances, the majority of which dissolve in water to form solutions which are acid in reaction. The pH of such aqueous solutions ranges between 4 to 7.0, depending upon the base and the acid used to form the salt. A variety of acids may be used to form the salts. Hydrochloric acid is most commonly used; the resulting salt is known as the hydrochloride. The choice of acid is made from the standpoint of pH of the resulting solution, solubility, crystal formation, stability, ease in handling of the salt (weighing). The basic form is liberated from the acid when the drug is injected into the tissues. The basic form enters the nerve and produces the physiological effect. Tissue fluids have considerable buffering capacity and, therefore, the base is liberated from solutions of salts if a solution which is not too acid is used. The pH of the salt becomes adjusted upward to the hydrogen ion concentration of the tissues into which it is injected Likewise the pH of an alkaline solution is brought down to the hydrogen ion concentration of the tissue. It was once believed that increased anesthetic activity resulted from alkalinization of solutions of local anesthetics to the point short of precipitation. This has not proved to be the case. The buffering action of the tissues adjusts the pH of the solution to that of the tissues. Alkalinization, therefore, is without effect if solutions are used for injection. However, potentiation does occur if the drug is applied topically because the mucous membranes are devoid of buffering action. Certain drugs, such as dibucaine or tet-

racaine have precipitating points close to pH 7 and may precipitate the free base when mixed with spinal fluid which is alkaline. Knight and his associates using cerebrospinal fluid noted that procaine mixed with spinal fluid which had a pH 7.2 precipitated at pH 9.4 when sodium hydroxide was added; dibucaine gave a pH 7.4 and precipitated at pH 8.35; tetracaine gave a pH 7.2 and precipitated at pH 8.10; piperocaine gave a pH 7.15 and precipitated at pH 8.75. The salts had a pH as follows: procaine 5.35, dibucaine 6.02, tetracaine 5.30 and piperocaine 4.0.

Local anesthetics are usually ineffective when injected into inflamed areas. Several explanations are offered for this behavior: (1) Absorption is increased from the injection site due to the hyperemia caused by the inflammation. (2) The tissues are acid in reaction due to the acid products liberated by the disease process. The base which is the effective form of the drug fails to be liberated.

The salts of sulphuric, formic, mucic, lactic and boric acid are sometimes used instead of hydrochloric. The pH of their aqueous solutions differs from those of the hydrochloride.

SIMILARITIES TO ALKALOIDS

Alkaloids are organic amines derived from plants. Local anesthetics, since they too are amines, are similar to alkaloids. They respond to the same tests and show similar chemical responses, such as precipitation, salt formation, color reactions, etc. Solutions of picric acid, gold chloride, iodine, potassium mercuric iodide and such combinations, known as *alkaloidal reagents*, cause precipitation of distinctive colored, crystalline compounds which may be used for qualitative identification (Chap. 16).

BIOLOGICAL AND BIOCHEMICAL ASPECTS OF LOCAL ANESTHESIA

The mode of action of a local anesthetic once it enters the nerve fibre is not known in spite of the intensity with which study of this subject has been pursued. Early workers attempted to correlate the blocking effects of local anesthetics with narcosis produced by general anesthetics and to associate the same mechanism of action for both types of drugs. It has been well established that the mechanisms involved in each case are different. Nonetheless, certain data which was accumulated in these early studies are of interest and may have some practical significance.

LIPOID SOLUBILITY

It was once believed that local anesthetics obeyed the Overton-Meyer rule (Chap. 27) because the bases manifested varying degrees of lipoid solubility and were relatively insoluble in water. However, data of Löfgren and other workers indicate that the Overton-Meyer rule is not valid for local anesthetics. Löfgren determined the distribution coefficients of 22 local anesthetics in oleyl alcohol-water systems. These compounds were of the aminoacyl amide type and were compared with procaine. No correlation could be found between the distribution coefficients and anesthetic potency. The Overton-Meyer rule applies to inert substances. Local anesthetics are not chemically inert. The rules does, however, apply to general anesthetics when they are applied directly to nerve fibres and induce local anesthesia. Isolated nerves exposed to ether, chloroform and other volatile anesthetics produce a blockade also. The concentrations necessary to

produce such a blockade are far greater than those necessary in circulating blood when these drugs are used to induce general anesthesia. The blockade produced by conventional local anesthetics probably results from the effects of the drug on the lipoprotein film at the surface of the plasma membrane. The lipoprotein film, as has been mentioned previously, is composed of metallic ions, neuroproteins and lipoids. Presumably the metallic ions are the instruments for conduction. Local anesthetics have active groups and act by polar association. By this is meant that the hydrophilic pole becomes oriented into the aqueous phase and the aromatic hydrocarbon residue into the lipoid phase of the membrane proper. Indifferent narcotics such as ether and chloroform, probably exert their effects by Van der Waal's forces (Chap. 27).

SURFACE TENSION AND ABSORPTION

Attempts have been made to associate activity and potency with physicochemical phenomenon. Much of the data available indicate that whatever changes are caused by a local anesthetic in a fibre occur at the surface of the fibre. Data to support this was obtained in some of the early experiments on narcosis. There appears to be some correlation between the ability to lower surface tension and anesthetic activity but this is not a consistent finding and no generalization can be formulated. The addition of local anesthetics to oil/water systems in vitro causes a lowering of interfacial surface tension. These observations have in the past been used to support the theory that lowering of surface tension causes narcosis. Local anesthetics are readily adsorbed to activated surfaces. In vitro, local anesthetics are adsorbed to nega-

tively charged particles, such as those of activated charcoal. This is also true of many alkaloids also. The degree of adsorption at a solid-liquid interphase generally parallels narcotic potency of a series of drugs.

PROTEIN COAGULATION

The effects of local anesthetics upon the intracellular protein was once believed to be similar to that produced by general anesthetic drugs. Reversible, ultra-microscopic coagulation of protein within the cells has been reported. This, however, may be a manifestation of toxicity since the quantities necessary to produce this effect are far greater than are ordinarily used clinically.

INFLUENCE OF MYELIN SHEATH ON CONDUCTION

Some nerve fibres are surrounded by a sheath of myelin which is enclosed in a histologically distinguishable membrane called the *neurolemma*. The myelin is interrupted at intervals of one mm. or less into sausage-like segments. At these points myelin is absent and the sheath dips down to and makes contact with the axone. These interruptions are called the *nodes of Ranvier*. The myelin acts as an insulator for the nerve fibre and increases efficiency of conduction by conserving energy. Local anesthetics do not penetrate the myelin and can, therefore, pass into nerve fibres only at the nodes of Ranvier. They do, however, readily penetrate into unmyelinated fibres. Anesthesia is established sooner and with less concentrated solutions in such uninsulated fibres.

INTERFERENCE WITH HUMORAL MECHANISMS

The mechanism by which local anes-

thetics stabilize the membrane is not known. One thought is that some humoral substance, possibly acetyl choline, normally mediates the changes in permeability and permits the migration of ions during transmission of the action potential. Local anesthetics, acting by competitive inhibition, prevent the changes in permeability by competing with the receptors for acetyl choline in the neural membrane. The structures of many local anesthetics bear some resemblance to that of acetyl choline. Data in support of this idea are not convincing.

Another thought is that the local anesthetic may act by competing with specific enzymes for the activation and completion of a chain reaction which causes the release of energy necessary to effect the ionic migration which occurs across the membrane. Acetyl choline likewise is involved but in this case initiates the release of energy from high energy phosphate bonds (Chap. 27). The energy causes the release of acetyl choline from the adjacent areas so that the reaction is relay-like. Evidence exists that local anesthetics alter metabolism of nerves. The oxygen consumption and utilization of glucose, for example, are inhibited by procaine and cocaine. The output of carbon dioxide is decreased and the output of ammonia is increased. The relationship of this depression of metabolism to the causation of the block is not known.

THRESHOLD CONCENTRATIONS AND "FIXING"

A minimal or threshold concentration must surround the fibre to cause a blockade. Concentrations weaker than this are without effect. The perineural concentration necessary to produce a block is many times the tolerable plasma level.

The drug requires time for passage into a nerve fibre but relatively speaking passes very rapidly into the membrane due to the high external gradient. The rate of entry varies with the chemical nature of the drug, the concentration and the type and size of the fibre. Thus, there is a latent period from the moment the drug is applied until a blockade is established. After the injection the drug is carried away by the lymph and the perineural concentration gradually falls. As soon as the perineural concentration falls below the intraneural level, the drug begins to re-enter the lymph. Conduction is re-established as soon as the concentration is below the threshold value. The threshold value differs for each drug under a uniform set of experimental conditions. Conduction is "all or none" without decrement. In other words the blockade in a partially narcotized area is as complete as in the completely narcotized area and continues so until the concentration falls below the threshold level and the membrane is restored to its active state. Exceeding the threshold concentration does not increase the intensity of the block since it is "all or none." It may, however, prolong the block somewhat because more time is required to carry the additional quantity from the perineural area. The increase in duration is not proportioned to the increase in amount. For example, doubling the quantity applied does not double the duration.

The passage of the drug into the fibre and its union with whatever receptors are involved in conduction with the subsequent establishment of the blockade is often referred to as "fixing" by clinicians. The term is misleading because it infers that some irreversible chemical union or binding occurs. Little is known of the in-

teraction that occurs at the molecular level between protoplasm and local anesthetics. The bonding, whatever it is, is reversible.

IONIZATION AND NARCOSIS

Narcosis is caused by the undissociated molecule of the free base. In general, the free bases of most local anesthetics are poorly ionized. As a rule the salt is more highly ionized. The cation is positively charged and is the same in both cases. The ionization is represented as follows:

$$NR_4OH \rightarrow NR_4{}^+ + OH',$$
$$NR_4Cl \rightarrow NR_4{}^+ + Cl'$$
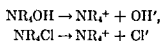
Krahl, Kaeltch and Clowes studied the inter and extracellular pH of arabica eggs. The pH of the intracellular protoplasm is lower, that is, it is more acid, than that of the extracellular medium surrounding the cell. Equilibrium concentrations of both the cations and the total base inside the cell are in excess of those outside it. Immersing the eggs in solutions of the free bases of local anesthetics was followed by penetration of the undissociated molecules into the cell. Presumably the local anesthetic action is due to the intact undissociated molecule and not the ion.

Saturated solutions of the free bases are less concentrated than solutions of the salt because of the relatively lower water solubility of the base. As the pH increases a point is reached at which the base begins to precipitate. This point varies for each drug. For procaine it is above 8.4.

POTENCY AND DURATION OF ACTION

The clinical usefulness of a local anesthetic drug depends upon its potency, duration of action and toxicity—both local and systemic. Potency and duration of action are related but do not necessarily parallel each other. Potency refers to the quantity necessary to effect the physiological change. Tetracaine, for example, is ten times more potent than procaine. One-tenth the quantity is necessary to block conduction under identical circumstances. The duration of the block is nearly twice that of procaine. Quantity and duration, therefore, are not directly related. Both potency and duration of action vary with the chemical configuration of the molecule since diffusability, adsorbability, orientation of the molecule at the lipoid-water interphase and ease of destruction are related to molecular structure.

LATENT PERIOD

It has been mentioned that a latent period of several or more minutes elapses from the moment the drug is applied until blockade occurs. The periods of latency increase progressively as the duration of action increase. Thus, dibucaine has a longer latent period than tetracaine, which in turn has a longer one than procaine. Data concerning time of onset obtained in vitro using isolated nerve preparations differ from those obtained clinically. Clinically the drug is injected into the tissue surrounding the nerve while experimentally the drug is applied directly to the fibres. The drug becomes diluted with the perineural tissue fluid. The greater the distance between the point of injection and the nerve the greater the dilution. Then, in addition, some of the drug is carried away by the blood and lymph. Therefore, variable results are obtained in studies in the intact animal or in man since all conditions are not fixed and concentration is uncontrollable. The

concentration of the injected solution must be greater than the threshold concentration necessary for an effective block. Data using isolated nerve preparations are more precise and present a more realistic picture from an experimental point of view.

SELECTIVITY OF ACTION

A difference in susceptibility of various types of fibres has been observed clinically. Autonomic and sensory fibres are affected before motor. This was once ascribed to differences in chemical composition of the various nerve fibres. This, however, was an erroneous assumption. It has been well established that this behavior is in no way related to chemical differences but that fibre size plays the dominant role in the variations in susceptibility. The sensory and autonomic fibres are smaller than the motor and are, therefore, affected first. Erhenberg has noted that the time required for induction of a blockade by a particular drug varies inversely with the concentration of the drug and directly with the square of the radius of the nerve. Correlation between penetration and anesthetic activity is not uniform. Procaine, lidocaine and ravocaine show equal penetration but different activity and duration when compared on a basis of molar concentration. Likewise, there is no strict correlation between speed of penetration and duration of action. Other factors are involved, most important of which are local destruction of the drug. Generally the long lasting drugs are destroyed more slowly than brief acting. Dibucaine, one of the longest acting is not hydrolyzed by the tissue enzymes.

INACTIVATION IN THE NERVE

The majority of local anesthetics are esters. They, therefore, undergo hydrolysis to a carboxylic acid and an amino alcohol. This occurs both in vivo and vitro. The hydrolyzed products are nonanesthetic. Compounds in which the bonding is of the amide type likewise undergo a hydrolytic type of cleavage. The resulting products in this type of cleavage are an amide instead of an acid and an amino alcohol. Inactivation is carried on in the liver to a large extent and is aided by enzymes. The ease of inactivation bears some relationship to the duration of action of the drug. As a rule, the longer lasting drugs are hydrolyzed more slowly than the rapid acting. More will be mentioned about detoxification later on. Longer lasting drugs appear to diffuse in and out of a nerve fibre more slowly than the shorter acting. It is not unreasonable to suppose that these two factors combined may explain the prolonged duration.

CUMULATIVE EFFECTS IN NERVES

Bathing a nerve fibre with Ringer's solution fails to remove the drug completely. The block, therefore, persists as long as the concentration exceeds the threshold value. Procaine appears to be washed from the fibre more easily than tetracaine. Dibucaine is also removed with greater difficulty than procaine.

The outward diffusion of a local anesthetic from the fibre occurs gradually. Recovery occurs when the intraneural concentration of a drug falls below its threshold level. Some drug still remains in the fibre even though conduction has been restored. The blockade may be reestablished by adding the difference between the amount present and the threshold value. If the re-application is made several hours after recovery the original threshold concentration is necessary.

This is presumptive evidence that none of the drug is present in the fibre at this time.

ABSORPTION AND CONCENTRATIONS IN BLOOD

Concentrations of local anesthetics in blood and tissue are not easily measured due to the fact that specific tests are lacking and the quantities dealt with are minute. The perineural concentration of a local anesthetic necessary to cause an effective blockade is many times greater than a tolerable blood level. Such concentrations if allowed to accumulate in the plasma would cause serious systemic reactions. During nerve anesthesia, at surgical levels, a peripheral nerve remains excitable and continues to transmit impulses. The concentration necessary to depress the neurons of the central nervous system is far less than that required to cause a blockade of a nerve peripherally. The concentration of a local anesthetic in the blood which produces central depression is considerably less than that necessary perineurally to effect a blockade. Systemically the local anesthetics are highly toxic. For this reason local anesthetics are deposited in as small an area and are localized as close as possible to a nerve trunk. The total quantity is limited to the minimum necessary for effective anesthesia. The ratio and degree of absorption of a local anesthetic depends upon the vascularity of tissues at the site of injection. When a drug is injected into a highly vascular area, as for example the scalp, the duration of action of anesthesia is brief (less than 10 minutes with procaine). Injection into the skin of the back where the blood supply is poor results in anesthesia which lasts 45 minutes or longer. The longer the local anesthetic drug remains at the site of injection the longer the block.

Local anesthetics are rapidly absorbed from the mucous membranes and serous surfaces. Blood levels comparable to those obtained during intravenous infusion may be attained when they are topically applied. Local anesthetics are not absorbed from the unbroken skin. Absorption is much slower from the subcutaneous tissues than the muscle. After subcutaneous injection of comparable weights of tetracaine and cocaine blood levels are barely detactable. However, if they are applied to the mucous membranes of the nose and trachea, the blood levels rise rapidly to about half of those obtained after rapid intravenous injection. Absorption and passage into the blood is slowest from the intrathecal space. Absorption from the peritoneal cavity is almost as rapid as if the drug were given intravenously. Regardless of the site of injection all local anesthetics ultimately pass from the tissues into the blood stream and thence to the liver or kidney after which they are eliminated or detoxified.

DETOXIFICATION

The ester and amide type of local anesthetic drugs are partially or completely detoxified by the tissues of the body. Unmetabolized portions are eliminated unchanged into the urine by the kidney. Detoxification is accomplished almost entirely by the liver. Some breakdown occurs in muscle, nerve, blood and other tissues. The chemical reactions involved are hydrolysis followed by conjugation of the acid. Detoxification is accelerated by enzymes in the liver, blood and other tissues. The hydrolysis of procaine, for example, is catalyzed by a group of several enzymes called *pro-*

caine esterase into para-aminobenzoic acid and diethyl amino ethanol. Procaine esterase is believed to be identical to the pseudo cholinesterases. The serum pseudo cholinesterases are *not* specific for procaine, since they hydrolyze other esters, such as acetylcholine, tetracaine, chloroprocaine, succinyl choline and so on. Physostigmine (eserine), which is a cholinesterase inhibitor, retards the hydrolysis of procaine in vitro. In the intact animal, however, anticholinesterases appear to exert little or no effect on the rate of hydrolysis of local anesthetics. The rate of detoxification depends upon the metabolic state of the individual receiving the drug. Whether or not this is due to variations in activity of the enzymes has not been established with certainty. The levels of both true and pseudo cholinesterases are decreased in certain disease states. For example, a decrease in hepatic function is common in patients with toxic goiters, anemias, and diseases due to inadequate nutrition. This may result in low plasma cholinesterase levels. Detoxification of local anesthetics, therefore, may be delayed if used in their presence or if impaired liver function is present.

An undetermined amount of non-enzymic breakdown of a local anesthetic occurs in vivo. The amount varies from tissue to tissue and with each drug. The para-aminobenzoic acid resulting from the breakdown of procaine is either conjugated with glycine to amino hippuric acid, methylated to para methyl aminobenzoic acid, or is eliminated unchanged in the urine. The three reactions may occur simultaneously. The conjugated products also are eliminated into the urine. Approximately 25% of the alcohol fraction of procaine (diethyl amino ethanol) is excreted unchanged into the urine.

Presumably, the remainder is metabolized in the body. The hydrolysis of procaine occurs rapidly. A fatal intravenous dose (in a cat) is hydrolyzed within 20 minutes. Halogenation of procaine increases the rate of hydrolysis. Procaine is hydrolyzed at ⅔ the rate of 2,chloroprocaine. An increase in rate of hydrolysis also occurs with 2,bromprocaine, 3,5, dichlorprocaine and 2,chlorthiocaine. Apparently halogenation facilitates enzymatic hydrolysis. The majority of para-aminobenzoic acid esters are hydrolyzed partially or completely in the body. Tetracaine is hydrolyzed at ⅓ the rate of procaine. The more complex esters of other acids, as for example cocaine and the amides such as dibucaine, are hydrolyzed with greater difficulty and partially eliminated unchanged through the kidney. Hydrolysis occurs at a slower rate. Lidocaine is very stable and slowly hydrolyzed in vitro. In vivo, however, the breakdown is more rapid. The aromatic ring is converted to a hydroxy compound which is conjugated with sulphates. In four hours less than 3% appears in the urine. Piperocaine is hydrolyzed at ⅛ the rate of procaine.

Studies on the detoxification of local anesthetics have been performed almost exclusively in animals. Data on the metabolic fate of many drugs in man are not available due to the difficulty in carrying out experiments during clinical use. Results of animal studies do not necessarily apply to man. Dogs and humans, for example, excrete cocaine unchanged into the urine while rabbits detoxify the drug completely by hydrolysis into ecgonine and benzoic acid. The hydrolysis occurs in the liver.

Drugs which are destroyed or eliminated slowly are, as a rule, more toxic systemically than those which are easily

detoxified. Practically speaking the safety of most local anesthetics depends upon the balance between the absorption of the drug into the blood stream and its removal from the blood by destruction, storage or excretion into the urine. In general, the ester type compounds are more easily hydrolyzed than those which have amide or ether type linkages. The fate of hydroxy type compounds has not been studied, presumably because they are used so little and they arouse little interest. Obviously, since they are not esters they cannot undergo hydrolysis.

METHODS FOR EVALUATING THE EFFICACY OF LOCAL ANESTHETICS

The clinical efficacy of local anesthetic drugs is evaluated by pharmacological and not by chemical methods. The value of the data obtained varies with the method used. Data obtained by one method may be compared only to data obtained under identical experimental conditions. The confusion and misunderstanding which exists concerning local anesthetics is due to attempts to compare data obtained under dissimilar experimental conditions. Data of one investigator employing one technique have been compared with those of another using a different method. The concentration of the drug, the time interval from the moment of application to the onset of narcosis, the duration of narcosis and the type and intensity of the stimulus used to test the narcosis, are important factors to record in such studies. Differences in chemical nature of the drug, physicochemical properties and external experimental conditions, such as concentrations, degree of ionization and pH may cause variations in response. Body temperature, temperature of the injected solution, the size of the area of injection and duration of contact of the drug with the nerve are all important factors which also are often varied and should be standardized. One drug may be applied to a nerve for five minutes, but, due to slow penetration, maximal action is not attained in that time. A short acting drug may attain its maximal effect in this time interval but the duration of action may be longer than that of an ordinarily longer acting because this overall duration of contact may be longer.

Cocaine was formerly the standard of comparison for studying all the actions of local anesthetic drugs. However, cocaine is no longer used for infiltration; therefore, procaine has become the drug for comparison of injectable anesthetics. Cocaine, however, is still used as the standard for comparing the topical effects of local anesthetics since procaine is devoid of topical action.

THERAPEUTIC AND LETHAL DOSES

In order to evaluate the worth of a drug it is necessary to know the minimum therapeutic dose and the minimum lethal dose. The minimum lethal dose expressed over the minimum therapeutic dose results in the ratio known as the *therapeutic coefficient* of the drug.

THE EFFECTS OF DRUGS ON TISSUES

SOLUBILITY

As is the case with other anesthetic drugs the action of local anesthetics is reversible. After the drug is removed from the neuron normal function is restored with no visible structural or functional alteration. Besides, possessing reversibility it is important that a drug

exert no deleterious effect on surrounding tissues. Hundreds of drugs have been synthesized which possess local anesthetic activity but have been discarded because they caused local irritation or were toxic systemically. Sloughs of the soft tissues have been reported following the infiltration of easily precipitated drugs. Dibucaine and drugs of the quinine type have been objectionable in this respect. Some of this irritation may be due to poor water solubility at the pH of the tissues. It has been suggested that during infiltration anesthesia the crystals precipitate in the tissues and act as a foreign body. Insoluble anesthetic drugs, such as benzocaine possess some water solubility but not enough to be used for infiltration.

Transitory or even permanent damage to tissues has resulted from improperly prepared solutions of the currently used drugs. Destruction of tissues has resulted from using either highly alkaline or highly acid solutions. Generally most local anesthetics are used in the form of the salt. The pH of the salt is anywhere from 4 to 7.0. Solutions having a pH less than 3 or 4 or greater than 6.8 are more irritating. Procaine hydrochloride at pH 4.0 is irritating when injected. Procaine borate is alkaline in reaction due to the fact that boric acid is a far weaker acid than hydrochloric acid. The solutions of the borate have a pH of 8.1. Procaine borate has caused pain during injection in a considerable portion of the patients. However, in clinical trials it has been found that the more acid solutions have caused more pain and irritation to tissues than the alkaline.

TONICITY OF SOLUTIONS

Another factor of importance in considering the effects on tissues is the osmotic effect of local anesthetics. Tissues ordinarily possess an osmotic pressure equivalent to that of a 0.9% aqueous sodium chloride solution. Aqueous solutions of salts of local anesthetic drugs may exert an osmotic pressure greater or less than that of tissues depending upon the concentration. Hypertonic or hypotonic solutions injected into tissues disturb the osmotic equilibrium between the cell and the external environment. Water diffuses from the cell when hypertonic solutions are used so that shrinkage of the cell results. These changes may be followed by death or partial loss of function of the cells. A hypotonic solution causes a similar attempt to adjust the disturbed osmotic relationship. Water diffuses inward and the cells swell. Hypotonic solutions are less deleterious than hyper since they do not attract solids from the cell. A 4% aqueous solution of procaine exerts an osmotic pressure equivalent to that of the cells. Solutions of procaine ordinarily employed clinically range in concentration from 0.5% to 2%. They are, therefore, hypotonic and theoretically not physiological unless salt is added to bring them to normal osmolarity. A mixture of 0.45% sodium chloride and 2% procaine forms an isotonic solution. Potent drugs such as dibucaine or tetracaine offer less of a problem than procaine, piperocaine and drugs of like potency because the amount used is small and their osmotic effect is negligible if saline solutions are used as the solvent. Whenever possible isotonic solutions should be used. Hypertonic solutions are less desirable than hypotonic solutions.

CONCENTRATED SOLUTIONS

Concentrated solutions may cause damage. In spinal anesthesia in dogs

strong concentrated solutions of procaine caused changes in the ganglion cells. Lundy and Essex noted changes in spinal cords of dogs when concentrations of 12½% and upwards were used. Other workers have reported neuritis, paresis or necrosis following both spinal anesthesia and local nerve blocks with various drugs. A combination of anesthetic drugs and sympathomimetic amines, such as epinephrine has been known to cause slough, particularly if peripheral vascular disease is present. It seems likely that the vasoconstrictor causes an ischemia which is followed by necrosis.

RELATIONSHIP OF CHEMICAL STRUCTURE TO TOXICITY

Toxicity from local anesthetics is of two types, *local* and *systemic*. Systemic toxicity is manifested by convulsions and depression of the cardiovascular system. Systemic effects develop when a local anesthetic is rapidly absorbed or is used in amounts which cause a relatively high plasma level. Ordinarily the plasma levels are barely detectable after perineural injection. Toxic reactions are invariably due to overdosage.

Some correlations can be made between chemical structure and systemic toxicity. Some of these have been described earlier in the chapter. Generally the potent, clinically useful, injectable anesthetics are all convulsants and cardiac depressants. Beutner and Calesnick have pointed out that all the efficient local anesthetics stimulate the cortex and that the convulsive power in most instances parallels their activity. In spite of statements made to the contrary, the clinically useful local anesthetics, with a few unimportant exceptions, conform to the general configuration of hydrocarbon, an aliphatic pivot (isoteric group)

and an amino group. Departure from this configuration tends to produce drugs which are less efficient and locally irritating from a clinical standpoint. The alcohol type of drug (benzyl alcohol), the antihistamines, most of which are phenylenediamines, the cupreines (Eucupine) and the barbiturates are drugs capable of causing a blockade but have structures which depart from this general molecular configuration. Their efficiency as local anesthetics leaves much to be desired. They cause considerable local irritation, and, as a rule, little convulsant activity.

LOCAL TOXICITY

Many local anesthetics have been prepared and studied which are unsuitable because they cause irreversible changes in nerve and perineural tissues. These drugs have a necrotizing effect. Injury, due to mechanical factors (needles, pressure) to the nerve and surrounding tissues may be an additional factor which is superimposed on the direct injury caused by the drug. It is possible for the free base of local anesthetics to be precipitated in tissues due to alkalinity of tissue fluids. Decomposition of the crystals in the tissues excites a foreign body reaction. The conventional drugs which are used clinically do not do this, however, because most of them precipitate at pH above 7.4. Slough due to dibucaine has been reported. This drug precipitates at a lower pH than procaine. Possibly precipitation could be a causative factor.

Aqueous solutions of the salts are acid in reaction and, thus are capable of interacting with metals. Local irritation has been reported due to such interaction with the metal of plungers and other parts of syringes which comes in contact with the solution. Irritation may be

caused by the solvents used to suspend drugs of low solubility which are prepared with oils and water soluble solvents, such as propylene and polyethylene glycols. Solutions of local anesthetics in this type of solvent have been used to produce long lasting anesthesia. Actually few truly reversible local anesthetic drugs produce a block lasting more than 2½ to 3 hours. Blocks longer than 2½ hours are only obtained by the use of some potentiating agent. Usually a vasopressor such as epinephrine or norepinephrine is used to retard absorption so that a longer period of contact is made with nerve tissue. Intense vasoconstriction resulting from use of these agents has caused slough. The addition of electrolytes such as potassium salts (sulphate or chloride) for potentiation has likewise caused edema and slough.

As a rule, the majority of injectable local anesthetics cause no permanent neural or perineural injury. Pizzolato, Mannheimer and the writer have studied the effects of procaine, tetracaine, lidocaine, chlorprocaine, dibucaine, piperocaine, and hexylcaine in aqueous solutions upon the sciatic nerve and the soft tissues of the rat. Hexylcaine, hydrochloride (Cyclaine) and piperocaine (Metycaine) cause transient changes in the nerve. Similar results have been reported by others. It may be possible that the irritation is due to the high acidity of these solutions.

Hyaluronidase

Hyaluronidase is a mucolytic enzyme which is added to solutions of local anesthetics to facilitate spread of the drug. The enzyme hydrolyzes a mucopolysaccharide known as hyaluronic acid which forms a barrier for the diffusion of fluid in the tissues. The enzyme breaks the barrier and facilitates the spread of local anesthetic solutions and accelerates the onset of anesthesia. The enzyme reduces viscosity of tissue fluids. It is found in spleen, testicular tissue and bacteria (streptococci and pneumococci). Its activity is measured in turbidity units. No changes were noted in subcutaneous tissues of rabbits injected with hyaluronidase. Observations were made over a period of months after injection. Kirby and his co-workers noted that solutions containing hyaluronidase caused redness which appeared within five minutes and some subjects experienced tenderness for 48 hours, but, it gradually receded after this time. In general, local reactions are few and transient. The anesthetic plasma level is greater when the enzyme is combined with a drug than when it is omitted.

LONG LASTING LOCAL ANESTHETICS

The majority of histological changes in nerve and perineural tissues are observed following the use of preparations alleged to cause anesthesia lasting many hours or days. Most drugs or drug combinations used for long lasting anesthesia do not act by stabilizing the membrane, as does procaine and similar drugs. Instead they act by causing temporary or even permanent neurolysis. The block is not completely reversible. Histological changes are evident for days after the onset of the block. Many of these preparations designed for long lasting anesthesia are solutions of the free base of some local anesthetics, such as procaine dissolved in oils or glycols. Some preparations (Effocaine) are solutions of insoluble drugs (Butescin) in glycols and oils. When these solutions are injected into the tissues water is abstracted from the

cells and passes into the solution and precipitates the drug causing a foreign body reaction. Cells undergo crenation which is followed by neurolysis.

The fact that oils could produce nerve degeneration was first demonstrated by Duncan and Jarvis. They studied the effect of certain agents on the facial nerve in cats. They mapped the area of anesthesia and correlated it with histologic changes of nerves. Three groups of local anesthetics in almond oil were studied. All contained benzyl alcohol in addition to the local anesthetic. The first was composed of 1½% procaine base, 6% butyl aminobenzoate and 5% benzyl alcohol. The second solution contained ½% Nupercaine, 10% benzyl alcohol, 10% ethyl alcohol and 1% phenol and a third contained 1% eucupin, 3% benzocaine and 5% benzyl alcohol. The first caused anesthesia lasting from three hours to three days. The second mixture caused anesthesia lasting two to twenty-one days and the third mixture lasted one hour. Oil alone caused no anesthesia. Examination of the tissues fourteen or more days after injection showed that necrosis of the muscle fibres was complete; the nerves had undergone Wallerian degeneration. When durations of less than 14 days were obtained degeneration of the nerve was less complete. In some of the cases in which anesthesia lasted only one hour no abnormal nerve fibres were noted microscopically. They concluded that oil soluble anesthetics are anesthetics only because they cause nerve degeneration. Benzyl alcohol used alone in a concentration of 5% or more causes well defined changes. Almond oil alone did not cause a change. Emory and Mathews studied the subcutaneous injection of oil in muscles. A tissue capsule developed around the oil after a few days forming an oil cyst which persisted as long as a year. Abscesses developed in 50% of the animals injected with almond oil. Sesame oil produced a thick endurable cyst. Corn, olive and peanut oils were less irritating than sesame and sweet oil. Almond oil and cotton seed oil were the most irritating. The oils became encysted in the tissues. Brown made similar observations. Leukocytes collected around the vessel walls and accumulated there. Wandering cells passed into the oil droplets. Corn oil produced the least intense reaction. This was followed by sesame, cotton seed and peanut oils

SOLVENTS FOR LOCAL ANESTHETICS

Propylene glycol and polyethylene glycol are frequently used as solvents for local anesthetics. These are viscous, water white, clear fluids miscible with water. Weatherby concluded the tissue changes noted when these agents were used were due to hypertonicity of the solvent rather than the inherent chemical properties of the chemicals in the oils. Mannheimer, Pizzolato and the writer noted extensive necrosis of the cellular elements in a muscle, nerves, perineural and connective tissues. Bromsalizol was the first anesthetic to be dissolved in polyethylene glycol and injected. Propylene glycol and polyethylene glycol are both dehydrating agents and are, therefore, capable of causing tissue injuries. Effocaine, a preparation containing procaine base 1%, butyl aminobenzoate 5%, procaine hydrochloride ½%, polyethylene glycol 2%, propylene glycol 78% and water 20% causes severe damage to tissues. Its use has been abandoned because it is irritating and causes necrosis of soft tissues.

Solutions of procaine base in methyl cellulose have been prepared for injection to produce prolonged blockade. Such preparations likewise are neurolytic and necrotizing. Higher molecular weight carbohydrates of the dextran type and synthetic liquid plastics, such as polyvinyl pyrrolidone have been used for solvents for procaine to prolong anesthesia by retarding absorption. They likewise cause local tissue reaction.

Yamamoto demonstrated that drug mixtures intended to produce prolonged anesthesia containing quinine necrotize nerve tissue. The reactions, resembling Wallerian degeneration, begin after forty-eight hours. At the end of twenty days the nerve is completely destroyed. Two percent benzocaine and 10% urethane dissolved in water is stable. Intramuscular injection causes necrosis and intense cellular infiltration. Anti-histaminics likewise cause irritation when injected. Stephen and his co-workers noted anesthesia to be satisfactory with tripelennamine (Pyribenzamine) but caused local injury to three of thirty-eight patients. Concentration of 4 to 5% caused erythema followed by necrosis in the skin wheal. Antistine produces severe nerve injury in concentrations as low as 1%. Leavitt and Code noted that intracutaneously it produced a burning pain which lasted several minutes in six out of ten individuals. Local edema, redness and sloughing with ulceration followed in ten days. Mannheimer and his associates noted that tripelennamine intraneurally caused severe neurolysis.

Absolute and 95% alcohol, aqueous phenol (6%) also cause a blockade by producing neurolysis. None of these neurolytic drugs, therefore, may be considered as true local anesthetics.

IDENTIFICATION

The detection, identification and quantitative determination of local anesthetics is not a simple matter, since many compounds of diversified structure are known. Analysis must be done on an individual basis, that is, a specific test must be devised for each individual drug. There are, however, certain reactions that apply generally to a prototype compound which is characteristic of all the members in a group of several compounds. The para-aminobenzoic acid derivatives have a primary amino group on the aromatic chain, for example, which permits diazotization and formation of colored compounds whose optical density may be determined with a colorimeter. The method of Marshall and Bratten based upon the diazo reaction employs sodium nitrite and sulphanilic acid to analyze procaine. The coupling yields a red dye which can be estimated quantitatively by means of a photoelectric colorimeter. This test, however, does not differentiate between the para-aminobenzoic acid which results from the breakdown of procaine by enzymatic hydrolysis and procaine itself. Both substances respond to the test. Brodie and his associates have modified this test by adjusting the pH to the alkaline side so that the procaine is extracted but not the para-aminobenzoic acid. Compounds which have a substituent on the free amino group do not respond to the diazo reaction. For example, tetracaine, which has a butyl group replacing a nitrogen atom on the amino, cannot be diazotized. The test, therefore, cannot be employed for the detection of tetracaine. Parethoxy derivatives (Intracaine), meta (Primacaine) and ortho (Peridocaine) aminobenzoic acid deriva-

tives likewise do not respond to the diazo reaction. Therefore, the test cannot be used for analysis of these compounds.

Recently introduced techniques utilize fluorometry. Many organic compounds absorb ultraviolet light. Each absorbs light of different wave lengths. Therefore, specific tests may be devised for individual drugs. Tetracaine, for example, absorbs ultraviolet light of a wave length of 330 mμ. The absorption of ultraviolet light is due largely to the aminobenzoate portion of the molecule. Therefore, both the hydrolyzed ester and tetracaine itself respond if the two are not separated. However, the butyl para-aminobenzoic acid fraction may be extracted with benzine at a pH of 3 or less. The tetracaine passes into the benzine layer since it is soluble in benzine at this pH, but the hydrolytic products are not and remain in the aqueous layer. Above pH 8 the situation is reversed. Tetracaine is not absorbed but the hydrolyzed products are. Each of these two substances may then be quantitatively analyzed. Similar techniques using ultraviolet light have also been devised for procaine, lidocaine and other local anesthetic drugs.

Another test is based upon the general reactivity of amines with dyes, such as bromthymol blue and methyl orange. Colored complexes form which are of a different color than the reagent dyes. Procaine, tetracaine, cocaine and lidocaine form such complexes. These can be extracted by organic solvents from an aqueous layer and determined colorimetrically. Tetracaine, for example, is quantitatively analyzed by adjusting the solution containing the unknown (protein free blood filtrate, etc.) to pH 6, adding a dilute alkaline bromthymol blue solution and extracting the complex

which forms with a mixture of ethylene dichloride (10) and toluene (90). The dye forms a yellow complex salt with tetracaine. This complex is soluble in the ethylene dichloride-toluene mixture and quantitatively extracted by it. The free thymol blue is insoluble in the solvent mixture and remains in the aqueous phase. The optical density of the complex is determined on a photoelectric colorimeter at 410 mμ.

Other non-anesthetic amines normally present in blood also form complexes with the dye. Therefore, when blood is used as a blank must be run as a control. The intensification of the color above that produced by the blood is assumed to be due to the local anesthetic.

Blood samples containing local anesthetics must be analyzed promptly or preserved with an enzyme inhibitor such as sodium arsenate otherwise the plasma esterases hydroyze the drug and the values obtained will be low. Methyl orange has been used for the determination of cocaine and lidocaine by this technique. The purity of a compound may be verified by determining the melting point and comparing it with the melting point of a mixture of the unknown and a known pure specimen. There should be no change in the melting point if the unknown specimen is chemically pure.

PREPARATION OF SOLUTIONS

Care should be exercised in preparing, storing and handling solutions of local anesthetic drugs. The salt is more stable than the base, as a rule, and is, therefore, used for preparing aqueous solutions. Crystals should be accurately weighed and dissolved in accurately measured volumes of solvents. Solutions sterilized by boiling should be restored to the original volume to compensate for

evaporation. Most local anesthetics are stable. A few are not. Unstable drugs (cocaine) which cannot withstand boiling or autoclaving should be added to water sterilized at its boiling point and boiled one minute longer.

Solutions should be prepared in clean glassware using pure distilled water or saline as the solvent. The slightest trace of alkali in some cases may precipitate and cause the decomposition of the drug. Stock solutions of highly concentrated drugs should be well marked so that they are easily identified to prevent accidents from overdosage. Solutions of certain drugs, as for example dyclonine, may be bacteriocidal in concentrations used for anesthesia. In vitro they kill many gram negative and gram positive pathogenic organisms. However, spores may not be as readily destroyed and, therefore, difficulties may arise if one relies upon self sterilization for asepsis.

VASOCONSTRICTORS

Epinephrine and related aromatic amines are frequently added to solutions of local anesthetic drugs to produce vasoconstriction so that absorption may be retarded. This prolongs anesthesia and reduces toxicity. Epinephrine is the most efficient of these vasoconstrictors. The epinephrine is added to the cold solution of local anesthetic at the time of use because epinephrine is heat-labile and cannot be autoclaved or boiled. Epinephrine is compatible with most local anesthetics. However, it is unstable and oxidized to quinones if aded to stock solutions which are permitted to stand any length of time. Discolored (brown) solutions of local anesthetics should be discarded. Vasoconstrictors chemically related to epinephrine, such as ephedrine, phenylephrine and cobe-

frine are more stable but not as effective. Ephedrine is stable and can be boiled. Cobefrine, norepinephrine and phenylphrine, however, are also unstable and undergo deterioration when added to solutions of local anesthetic drugs and are allowed to stand or are subsequently heated.

STERILIZING AMPULES AND SOLUTIONS

The crystals or the aqueous solutions of local anesthetics to be used for intrathecal injection are sterilized and dispensed in sealed glass ampules. It is customary to sterilize the exterior of the ampule prior to the intraspinal injection. For many years, the ampules of not only the anesthetic drugs but also ampules containing the adjunctive drugs such as ephedrine and dextrose have been sterilized by the cold sterilization technique. This consists of immersing them in bactericidal solutions, such as alcohol, phenol, mercuric chloride and similar bacteriostatic and antiseptic agents. Methylene blue, gentian violet and other dyes are used to color the solution so that the contents of the ampule become colored in the event of contamination by sterilizing solutions through possible microscopic defects in the glass. There are serious objections to cold sterilization. Cold sterilization obviously does not sterilize the contents of the ampule so that inadvertent contamination during manufacture is not overcome. Besides the agents may not be spore killers and the exterior will not be aseptic. Cold sterilization, therefore, is being discarded and autoclaving is being adopted. Heat sterilization obviously eliminates the possibility of contamination of the contents of the ampule with the sterilizing agent. This technique, however, in-

troduces the possibility of deterioration of the drug. The time necessary to sterilize ampules has not been standardized and the amount of deterioration which single and consecutive sterilizations may cause is not known. In some institutions it is customary to sterilize the ampules together with syringes and needles which are to be used for the spinal anesthetic. There is little objection to this practice if the set of instruments is autoclaved only once. A decrease in potency is likely should any of the agents be re-autoclaved. Ampules of dibucaine, tetracaine and epinephrine (1:1000) showed no change in potency after autoclaving 5 to 15 times at 120°C. for 30 minutes. However, epinephrine autoclaved 15 times showed reduction in potency of at least 25%. Lidocaine apparently is stable and stands autoclaving. Dibucaine and tetracaine have been shown to have a diminution in potency when autoclaved at higher temperature. Procaine autoclaved at 250°F. for 15 minutes and then re-autoclaved for 15 minutes showed some deterioration but more than 85% of the original procaine content remained unchanged.

Recently the technique of dry sterilization using ethylene oxide mixed with carbon dioxide mixtures (10% ethylene oxide and 90% CO_2) have been used for sterilization. The carbon dioxide reduces explosive hazards. These gases are introduced into a vacuum in which the ampule with the drug has been placed until a pressure of 33 lbs. per. sq. in. is reached. At room temperature this procedure requires about 16 hours for sterilization but by increasing the temperature to 100–140°F. and the pressure to 100 lbs. the time has been shortened.

POTENTIATION

The duration of action and activity of

local anesthetics may be enhanced by the addition of non-anesthetic substances. Such an enhancement is referred to as potentiation. The type of agents capable of causing the changes are described below.

ORGANIC BASES

Various organic substances enhance the effect of local anesthetics. Quinine derivatives, caffeine and theobromine hasten the onset and potentiate the activity of cocaine, procaine and similar drugs. The mode of action is not known. Possibly these substances alter permeability of the cell membrane and facilitate entrance of the drug into the cells. These substances are locally irritating and of little value for extending anesthesia clinically.

ORGANIC ACIDS

Organic acids, such as phthalic, hippuric and phenylbutyric potentiate the action of procaine. The observations have been made in the laboratory and are not clinically applicable.

NARCOTIC AND ANALGESIC DRUGS

Antipyrine added to solutions of cocaine and other local anesthetics potentiate their action. The addition of 3% acetylsalicylic acid (aspirin) also potentiates the action of procaine. Local irritating effects caused by these drugs offset the advantages obtained by this potentiation.

PROTEINS

The addition of proteins such as egg albumin, gliadin (protein from corn), increase the intensity and duration of action of local anesthetics. Gliadin has been added to procaine (Pitkin) to increase the specific gravity of solutions as

well as to potentiate its action. Some drugs cause precipitation of the added protein; therefore, they cannot be used. Tetracaine, lidocaine and butyn have been found to be incompatible with proteins. Blood plasma has been recommended as a solvent for procaine for spinal anesthesia to potentiate the activity and prolong its action. The advantage gained is not worth the effort.

CATIONS

A number of investigators, foremost of whom is Kochman, observed that ions of alkaline and alkaline earth metals, particularly those of potassium or magnesium block conduction and alter physiologic functions when applied to nerve fibres. Attempts to utilize these experimental observations clinically to potentiate local anesthetic action have been unsuccessful. Presumably they act by depolarization of the membrane. Potassium sulphate (1.8%) combined with 2% procaine hydrochloride has been studied by Tainter and his associates with disappointing results. No remarkable enhancement of anesthetic action was observed after infiltration. Signs of local tissue irritation such as itching, pain and redness were noted.

MIXTURES OF ANESTHETIC DRUGS

Combinations of two drugs, one of which has a rapid onset of action but a comparatively short action (procaine) combined with another whose onset of action is slower but whose action is prolonged (tetracaine) are employed by many clinicians. The purpose, of course, is to obtain immediate anesthesia with procaine which has a short latent period as well as prolonged anesthesia. Presumably each drug acts independently of the other. The effects appear to be additive.

ANTAGONISM

Depressant drugs, such as barbiturates, chloral, paraldehyde, avertin and morphine act as antagonists to the systemic responses of local anesthetic drugs and decrease the lethal dose. The action is pharmacological and not biochemical.

Drugs which can be applied perineurally to reverse the action of a local anesthetic drug are unknown. Once the block has been instituted it appears to persist until the drug is removed from the perineural area.

INDIVIDUAL ANESTHETICS

COCAINE

Cocaine was the first drug to be used for local anesthesia. Gaedicke (1855) first isolated the drug from Brazilian coca. Niemann, a pupil of Wöhler (1860) first purified the alkaloid. Koller and Freud noted its anesthetic properties and discovered its usefulness as a surgical anesthetic (1880). Hall (1884) and Halstead (1885) were the first to use it in America for infiltration anesthesia. Although the drug has been displaced by less toxic, more satisfactory non-habitforming compounds, it is still employed for topical anesthesia.

Sources

Cocaine occurs together with several other related alkaloids in the leaves of the coca shrub. This plant, a member of the species *erythroxylon coca*, is extensively cultivated in South America (Peru and Bolivia) and to a lesser extent in Mexico and the West Indies. It is in no way related to the cocoa plant which belongs to an entirely different species. The trees, which are propagated from seeds, grow to a height of seven or eight feet. Within eighteen months they begin to produce the alkaloids and continue to do

so for almost forty years. The leaves which contain the drug, are harvested in March, June and November and dried on woolen cloths. They are then extracted with water and the aqueous solution is treated with lead salts to precipitate tannic and other natural occurring acids. The excess lead is then precipitated by means of hydrogen sulphide. The drug is then precipitated by alkalinization and extracted with organic solvents. A yield of 1% of the weight of the leaves is considered good.

Chemical Properties

Cocaine is methyl ecgonine benzoate. The drug is available either as the free base or as the salt. The free base (U.S.P.) is a white, crystalline compound, bitter, slightly soluble in water (1 in 600 cc. at 25°C.), but very soluble in oil, alcohol, and other organic solvents. It melts at 96° to 98°C. Aqueous solutions of the base are alkaline to litmus and other indicators. Acids, such as hydrochloric, and sulphuric combine with it to form the common salts. The aqueous solution of the free base is readily hydrolyzed by heating or by being allowed to stand in air. Molds also decompose the drug. The hydrochloride (U.S.P.) is a colorless powder composed of transparent crystals which melt at 183°C. These salts are water soluble but insoluble in fats and fat solvents. Cocaine does not possess a primary amino group and, therefore, does not undergo the diazo reaction, as does procaine. It forms a complex dye with methyl orange which is soluble in chloroform. The formation of this complex is quantitative. It is extractable from an aqueous base at pH 7.2. The reaction, therefore, is used for the quantitative analysis of cocaine. Cocaine is levorotatory.

Detoxification

In man the drug is slowly detoxified by the liver by hydrolysis to ecgonine and benzoic acid, both of which may be recovered from the urine. Detoxification varies with the species. In cadavers, cocaine is quickly decomposed so that its presence may be detected only in fresh specimens. Both cocaine base and cocaine hydrochloride are included in the U.S.P.

DIBUCAINE (NUPERCAINE)

Dibucaine (Nupercaine, Percaine) introduced in 1929 (by McElwain) is the most popular and useful of a number of quinoline derivatives. Its chemical name is butyloxycinchoninic acid diethyl, ethylene diamide. Thus, it is not an ester but an amide. It is a long lasting compound, due in part to its slow destruction.

Properties

Dibucaine is a base which forms salts with mineral acids. The hydrochloride is the salt used most frequently. It is a white, tasteless, odorless powder which melts at 98° to 98°C. (the melting point is not sharp), and is very soluble in water (1 in 0.5 parts) and in organic solvents, such as benzine, acetone, and chloroform. It is insoluble in ether and oils. The free base is less soluble in water than salts but soluble in oils, fats, and ointment bases. Aqueous solutions of the hydrochloride have a pH 6.2 to 6.5. The free base is readily precipitated by alkalies and alkaline substances, such as carbonates and bicarbonates. Solutions must be prepared in distilled water and stored in alkaline free glass, otherwise the drug precipitates out due to the action of the alkali. A solution, known as Howard Jones' solution, consisting of 1 mgm. of nupercaine dissolved in 1.5 cc.

of 0.5% saline was once employed for spinal anesthesia. The solution is hypobaric (lighter than spinal fluid), having a specific gravity of 1.0025 at 25°C.

Toxicity

Dibucaine has a greater *absolute toxicity* than cocaine or procaine. The *relative toxicity* is less than that of procaine, however, since a smaller quantity is required for anesthesia. The drug is slowly detoxified in the body and slowly eliminated. Anesthesia with dibucaine is long lasting, 2 to 3 hours alone—3½-4½ with epinephrine.

Dibucaine forms a crystalline product with potassium perchlorate (8%) which melts at 132°C. The drug may be identified by this reaction. Dibucaine forms precipitates with the usual alkaloidal reagents. Inasmuch as it does not possess an aromatic primary amino group, it does not respond to the diazo reaction as do procaine and other amino benzoates. Dibucaine reacts with methyl orange and other dyes to form complex colored compounds. The reaction is quantitative. The complex may be extracted with chloroform at pH 7.2. An ointment containing the free base (1%) and an ointment base is known as "Nupercainal." Salts of dibucaine may be heated and are compatible with epinephrine hydrochloride.

Piperocaine (Metycaine)

Attempts to synthesize drugs similar in structure to but less toxic than cocaine lead to the study of a series of drugs derived from piperidine. Although a number of derivatives of this type have been prepared, piperocaine (Metycaine) was found most adaptable. Metycaine (also known as Neothesin) was first introduced by McElwain (1929). Piperocaine

is methylpiperidinopropanyl benzoate (Table I.21).

Properties

Piperocaine occurs as the free base or in the form of salts of mineral acids. The *hydrochloride*, which is the most commonly used salt, is a white, crystalline substance with a slightly bitter taste (M.P. 111° to 113°C.). The salt is quite soluble in water (1 in 1 at 20°C.) and reasonably so in chloroform and alcohol. However, it is insoluble in ether. Aqueous solutions of the salt are faintly acid. The free base, which is a white crystalline product, is precipitated by alkalies. The free base is highly soluble in oils and fat solvents.

Although the molecule possesses an asymmetric carbon atom, the drug as marketed, possess no optical activity because it exists in a racemic form. Solutions are *self-sterilizing.* However, they may decompose if allowed to stand but this may be prevented by preservation with chlorbutanol. Piperocaine is compatible with epinephrine. *Thiourea* may be added to prevent decomposition of piperocaine-epinephrine mixtures.

Piperocaine does not possess a free primary amino group and does not respond to the diazo reaction, as does procaine. Piperocaine is easily hydrolyzed into its alcohol and benzoic acid by boiling with alkalies. Piperocaine is listed in the U.S.P.

Procaine

Procaine was first synthesized by Einhorn (1905). He prepared a series of esters from para-aminobenzoic acid and found that this one offered the greatest promise of clinical usefulness. Procaine is also known as Ethocaine, Novocaine, Neocaine, Planocaine. Procaine had nu-

merous other names which fell into disuse. In the early years of regional anesthesia procaine slowly replaced cocaine for regional and infiltration anesthesia. It is now the standard of comparison of local anesthetic drugs. However, it too is slowly being supplanted by more efficient and more potent and toxic drugs.

Properties

Procaine is a base which forms salts with various mineral and organic acids. The base is a white, odorless, crystalline compound which melts at 59° to 61°C. The base is slightly soluble in water, but soluble in alcohol and chloroform and oils. A solution in peanut and other vegetable oils is used for attempting prolonged block. The *hydrochloride* is very soluble in water (1 gm. in 0.6 cc.), less so in alcohol (1 to 30) and chloroform. It is insoluble in oils and ether. The hydrochloride melts at 153° to 156°C. Aqueous solutions of procaine hydrochloride may be boiled at 100°C. or sterilized by autoclaving dry in ampules at 120°C. Sealed ampules of crystals may be autoclaved several times. If exposed to air for any length of time, solutions of procaine and its salts are decomposed by bacteria. Ampules containing the powder may be autoclaved several times without decomposition. Aqueous solutions of the hydrochloride (pH 6) and nitrate are acid in reaction. The borate forms solutions which are alkaline (pH 8.1). The alkalinity of the borate is due to the fact that boric acid is poorly ionized and, therefore, a weak acid. Hydroxyl ions predominate when the salt undergoes hydrolysis in solution.

Detoxification

A solution of procaine incubated with fresh minced liver is hydrolyzed into para-aminobenzoic acid and diethylaminoethanol. In vivo, the same reaction occurs. Dunlop first showed that although liver is the most important tissue involved in detoxification, other tissues may also take some part. Possibly 95% is detoxified by the liver. The resulting aminobenzoic acid is acetylated, conjugated with glycine or eliminated unchanged during the detoxification. Hydrolysis is aided by the pseudo cholinesterases. These enzymes have also been referred to as *procaine esterase*. Hydrolysis in vivo occurs rapidly. The fatal dose in a cat is hydrolyzed completely if infused over a period of twenty minutes.

Identification

The procaine molecule possesses both a primary and a tertiary amino group. Therefore, procaine responds to tests which identify amino groups. Procaine responds to the diazo reaction since it is a primary aromatic amine. Nitrous acid (produced by reaction of sodium nitrite with hydrochloric acid), procaine and betanaphthol if mixed together react to form a red dye. This color is not specific for procaine. However, it may be used to differentiate procaine from other local anesthetics which are not primary aromatic amines. The diazo reaction has also been used by Bratten and Marshall for the quantitative estimation of procaine. This has been described previously under the section on analysis. Both procaine and its metabolic byproduct are coupled to form dyes in the diazo reaction.

A deep yellow color results when procaine reacts with an alcoholic solution of vanillin and sulphuric acid and alco-

hol. A white precipitate forms when this reaction mixture is added to a solution of potassium and mercuric chloride. This precipitate re-dissolves in aqueous sodium phosphate to form a deep yellow solution. The entire reaction of color and precipitate formation is quantitative. The resultant colored solution may be matched in a colorimeter with potassium chromate solution of the standard for the quantitative estimation of procaine. Para-aminobenzoic acid does not produce this test. This test is specific for procaine and detects very minute amounts of the drugs in tissues and body fluids.

Picric acid, perchloric acid, iodine, potassium mercuric, iodide and other alkaloidal reagents form precipitates when added to solutions of procaine. Solutions of procaine are hydrolyzed and oxidized by chromic acid and potassium permanganate.

TETRACAINE (PONTOCAINE)

Properties

Tetracaine (Pontocaine) is derived from para-aminobenzoic acid. It is also known as pantocaine, and amethocaine. Tetracaine forms salts with various acids as do other local anesthetics. The hydrochloride, which has a bitter taste, is white powder which melts at 147–150°. The drug is stable in air. Aqueous solutions of the salt are almost neutral. The free base separates from aqueous solutions upon the addition of alkalies. The base is an oily substance (melting point 41–42°C.) but re-dissolves in acids. Since one hydrogen of the paramino group on the benzoic acid portion of the molecule is replaced by a butyl group, tetracaine differs from procaine and other amino benzoates and does not respond to the diazo reaction.

Stability

Tetracaine gradually breaks down at room temperature over a period of time with the formation of crystals of n-butyl para-aminobenzoic acid. This compound is nontoxic but also is non-anesthetic. The crystals separate out as a solution stands. They are visible to the naked eye.

Tetracaine is widely used for intrathecal injection. It is dispensed in aqueous solutions or in the form of hydrochloride crystals in sealed ampules. Tetracaine is hydrolyzed in the body to n-butyl para-aminobenzoic acid. The hydrolysis occurs more slowly than it does with procaine. The bulk of the detoxification is carried out in the liver.

Tetracaine is one of the most widely used local anesthetic drugs for spinal anesthesia. The drug is approximately ten times as potent as procaine and causes a block which lasts twice as long.

Tetracaine may be estimated quantitatively by forming a complex color with bromcresol purple. The reaction has been described under the section on Identification of Drugs (this chapter).

Tetracaine is precipitated at a lower pH than procaine, but at a pH above that of the body fluids.

Tetracaine withstands boiling, autoclaving and mixing with aromatic amines used for vasoconstriction.

LIDOCAINE (XYLOCAINE)

History

Lidocaine is a highly specific local anesthetic which has found wide application both as an injectable and surface anesthetic. The drug was first synthesized in 1943 by Löfgren. It was studied under the investigative name of LL-30.

Stability

Lidocaine is highly stable in vitro. It will endure eight hours boiling with 30% hydrochloric acid or lengthy heating with alcoholic potassium hydroxide. However, it appears to be attacked much more rapidly in the body. Up to 3–11% of the usual doses used for regional block in man were recovered in the urine within four hours. The liver appears to be the principal site of biotransformation. The drug is found in both the free and conjugated forms. McMahon and Woods believe that the aromatic ring in lidocaine is oxidized to a phenolic compound and then conjugated with a sulphate radical. Preliminary evidence indicates that the aromatic ring of lidocaine is hydroxylated in the 4 position.

Salt

The salt is not isolated from the solution. It is prepared in solutions by reaction of hydrochloric acid with lidocaine. The salt is compatible with epinephrine. Lidocaine is about twice as potent as procaine hydrochloride and twice as toxic.

Identification

Methyl orange forms a complex colored compound with lidocaine as does tetracaine. The dye is extracted by ethylene dichloride and estimated colorimetrically. The method was applied by Truant and his co-workers for the determination of lidocaine and biological materials.

Lidocaine is well absorbed when injected intramuscularly in the rat. The addition of epinephrine greatly retards its absorption and prolongs its action. One hour after lidocaine was given intramuscularly, the highest concentration was in the kidneys, lungs, spleen, fat, heart and brain at appreciable levels. Low levels were present in the liver and blood.

Lidocaine disappears rapidly from the blood when given intravenously. A small fraction of the administered drug is recovered from the excreta. The differences between reactions of lidocaine and procaine can be explained in part by the differences of their physiological disposition. Procaine is metabolized more rapidly than lidocaine, since the percent of the dosage recovered for procaine at each time interval is much less than that for lidocaine. Lidocaine has a higher affinity for fat tissue than procaine. The fat level is several times that of the blood level.

CHLORPROCAINE (NESACAINE)

Chlorprocaine has the same chemical structure as procaine except that a chlorine atom replaces hydrogen in position 2. Chlorprocaine is a white, crystalline water soluble powder, with a molecular weight of 370.2, its melting point is 173–176°C. Chlorprocaine is twice as potent as procaine for infiltration anesthesia. Onset of action is somewhat more rapid. Hydrolysis occurs more rapidly than with procaine. It is believed to be about half as toxic as procaine intravenously. Chlorprocaine is detoxified by the pseudo cholinesterases present in the blood, liver and other organs. The low relative and absolute toxicity is believed to be due to the rapid hydrolysis. It is destroyed in human plasma four to five times more rapidly than procaine and more rapidly than many other local anesthetics.

HEXYLCAINE (CYCLAINE)

Hexylcaine is a benzoate and is, therefore, allied to piperocaine and cocaine. Hexylcaine is 1 cyclo hexamino, 2 pro-

pyl benzoate. Its synthesis has been accomplished by Cope and Hancock. The hydrochloride is soluble in water to an extent about 12%. A one percent solution is stable to boiling, autoclaving and sterilization. The hydrochloride is a white bitter powder with a slight aromatic odor. It is freely soluble in alcohol and water. A 5% solution in water is slightly acid having a pH range of 4.1–4.7. Its potency is similar to procaine. Duration of action is longer and toxicity less.

DYCLONINE (DYCLONE)

Dyclonine is also known as Dyclone and Falicaine. The compound is a butoxy piperidine propiophenone. Therefore, it is both an amine and a ketone.

Dyclone is a white powder, soluble in water which forms a hydrochloride salt. Its potency topically applied is similar to cocaine. It is satisfactory if used topically only. It is too irritating for injection. The drug is not a convulsant. It has neither an amide or ester type linkage, but resembles the alcohol type compound in structure and behavior. The topical action requires 5–10 minutes to become established. It is hastened by alkalization of the solution, but this is not advised because the basic form of the drug is unstable. It is not altered or broken down in the body. The (hydro-chloride) salt must be stabilized with chlorbutanol. Concentrations greater than 1% topically have caused necrosis. It is bacteriostatic and self-sterilizing.

Drugs Affecting the Autonomic Nervous System

SYNAPTIC TRANSMISSION BY CHEMICAL MEDIATORS

THE AUTONOMIC NERVOUS SYSTEM is of interest from a biochemical standpoint because synaptic transmission of impulses is accomplished by means of chemical mediators. This process is often referred to as the humoral mechanism for transmission of impulses. The impulses pass along the axones to the synapses of both parasympathetic and sympathetic nerve fibers, from which the mediators are liberated. These, in turn, unite with receptors in smooth muscle of the viscera or in exocrine glands which they innervate. Augmentation and inhibition of activity are thus explainable on a chemical basis.

Manifestations of stimulation or depression of the autonomic nervous system are common during anesthesia. Counteraction of these effects by antagonists is often necessary to overcome ensuing technical difficulties of anesthesia or undesirable side effects. Suppression of mucous and salivary secretions, blocking the cardiac vagus with anticholinergic drugs, lowering of blood pressure by ganglionic blockade, elevation of blood pressure by the use of sympathomimetic drugs are some common examples. Consequently, drugs acting on the autonomic nervous system are important in anesthesia.

CHEMISTRY OF PARASYMPATHETIC ACTION

Loewi first demonstrated that vagal stimulation caused liberation of a choline-like substance at the postganglionic nerve endings in the isolated frog's heart. This substance caused a parasympathetic stimulation when perfused through other similarly innervated organs. Dale proved that the substance was *acetyl choline*. The response of acetyl choline was similar to that of another base, muscarine, discovered many years before. The significance of this is discussed later.

CHOLINES AND ACETYL CHOLINE

Choline is a quaternary base. Structurally it is trimethyl, beta-hydroxyethyl, ammonium hydroxide.

$$
\begin{array}{ccc}
H & H & CH_3 \\
| & | & | \\
H-C & -C-N & -CH_2 \\
| & | & | \\
OH & H & OH \; CH_3
\end{array}
$$
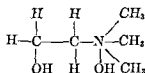
Choline

One may also consider it as ammonium hydroxide with three of its four hydrogen atoms replaced by methyl groups and the remaining ones by a hydroxyl and a hydroxy ethyl group. The substance, therefore, may be considered to be both a base and an alcohol. Choline is an important constituent of biological ma-

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terials of both plant and animal origin. It is abundant in bile and brain tissue. Interaction with acids causes esterification of the hydroxyl group on the beta carbon. The interaction of choline with acetic acid results in acetyl choline:
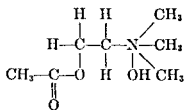
Acetyl Choline

Interaction with other acids or acid anhydrides results in a wide variety of esters, none of which is found in animal tissues. Many of these are physiologically active. Acetyl choline is the only choline ester found in animal tissues.

Exogenously, acetyl choline may be formed by reacting acetic anhydride with choline. Endogenously, it is synthesized in nervous tissue from acetic acid and choline aided by the enzyme choline acetylase.

Choline and choline esters, including acetyl choline, are bases and form salts with organic and mineral acids. The reaction may be likened to the formation of an ammonium salt from ammonium hydroxide and an acid:

$$NR_4OH + HCl \rightarrow NR_4Cl + H_2O$$
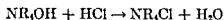
Acetyl choline chloride is the salt usually prepared for pharmaceutical use. The salts of choline are water soluble, hygroscopic and decompose easily. Solutions of the salt ionize into a quaternary ammonium cation and an anion:

$$NR_4Cl \rightarrow NR_4^+ + Cl'$$

Acetyl choline and choline both cause parasympathetic stimulation. Acetyl choline is anywhere from 50 to 10,000 times

more active physiologically than choline depending upon the locus upon which it acts. The quantities necessary for physiological activity are minute—one part in several million. The quantity is so infinitesimal that it is indicated in gammas (1/1000 milligram).

CHOLINESTERASES

Acetyl choline is rapidly hydrolyzed by naturally-occurring enzymes called cholinesterases. These enzymes quickly hydrolyze the ester to acetic acid to the less active choline. The exact number of cholinesterases present in the human body is not definitely known. Two basic types are recognized—*true cholinesterase* and *pseudo cholinesterase*. The two types may be distinguished by determining their specificity of action on various substrates. True cholinesterase hydrolyzes beta methylacetylcholine but not benzoylcholine. Pseudo cholinesterase hydrolyzes benzoylcholine but not beta methylacetylcholine. True cholinesterase has limited distributed. It is found at the endplate of skeletal muscle, in nervous tissue and in the erythrocytes. Pseudo cholinesterase is more widely distributed in the body being found in abundance in the plasma and other body fluids and non-nervous tissues. True cholinesterase is active at a low concentration of its substrate (acetyl choline) while the pseudo cholinesterases are active at high concentrations of their substrates. More than one type of each of the basic types have been identified (see Chap. 23). Pseudo cholinesterases hydrolyze procaine and other local anesthetics and succinyl choline and its several modifications.

Mode of Action of Esterases

Two sites of attachment of substrates

have been identified on the cholinesterase molecules. These are referred to as the *anionic* and the *esteractic* sites respectively. Attachment of substrates is at one or the other site or at both simultaneously. In the tissues the acetyl choline dissociates into a quaternary ammonium cation and an anion. The cation has an ionic head and a carbonyl head (portion carrying acetyl group). The ionic head becomes attached at the anionic site of the enzyme. The carbonyl group of acetyl choline becomes attached to the esteractic site, to form a labile, intermediate complex. This complex reacts with water to form acetic acid and choline after which the esteractic site is restored to its natural state. Substrates must become attached at the esteractic site before they can undergo hydrolysis. They need not become attached at the ionic site. Acetyl choline, however, requires attachment to both. Other quaternary ammonium ions are capable of combining at the anionic site to form compounds of varying stability. Some are bound more strongly than acetyl choline and prevent union with acetyl choline by prior attachment. Such substances, therefore, compete with acetyl choline for the enzyme and prevent the attachment of acetyl choline. Thus, the physiological effects of acetyl choline are sustained or accentuated due to failure of this mediator to be hydrolyzed. The enzyme may also be inhibited by compounds having a carbonyl head similar to that of acetyl choline. Such compounds attach at the esteractic site to form a more stable union than acetyl choline forms. The ester-grouping with these compounds is not activated as readily by water as is the case with acetyl choline.

TYPES OF ANTICHOLINESTERASES

Drugs which inhibit the activity of cholinesterases are known as *anticholinesterases*. Chemically three types of compounds appear to exert anticholinesterase activity both in vitro and in vivo: (1) the acetyl or aryl carbamates of which neostigmine is the prototype, (2) alkyl or aryl phosphates or alkyl fluorophosphates and (3) quaternary ammonium ions. Neostigmine has both a carbamino group and a quaternary cationic head and, therefore, reacts at the anionic and esteractic sites. This type of binding is stronger than that of acetyl choline but is reversible. The enzyme therefore is inactivated temporarily. Eserine (physostigmine) is a tertiary amine having a methyl carbamino group which combines reversibly at the esteractic site and thereby also acts competitively with acetyl choline for the enzyme (Table I.22). The alkyl phosphates such as diisopropylfluorophosphate and hexaethylfluorophosphate release phosphonium ion which combines at the esteractic site forming irreversible covalent bonds. The center is permanently inactivated by the di-alkyl phosphate radical.

Acetyl choline is re-synthesized by the aid of the enzyme, acetylcholase, which is present in the proteins of the terminal membranes of the nerve endings. Hydrolysis of acetyl choline occurs rapidly —within 0 2–0.3 of a millisecond.

PHYSIOLOGIC BEHAVIOR OF CHOLINESTERASE

Acetyl choline is liberated at numerous sites in the body. The most prominent sites are: (a) at the postganglionic endings of parasympathetic fibers (b) at endings of all preganglionic fibers as they synapse with postganglionic fibers, (c) at

TABLE I.22

$(CH_3)_3\text{-}N\text{-}CH_2\text{-}CH_2\text{-}OH$

CHOLINE

$(CH_3)_3\text{-}N\text{-}CH_2\text{-}CH_2\text{-}O\text{-}C\text{-}CH_3$ ‖O

ACETYLCHOLINE

$(CH_3)_3\text{-}N\text{-}CH_2\text{-}CH\text{-}O\text{-}C\text{-}CH_3$ | CH₃ ‖ O

ACETYL-BETA-METHYL CHOLINE (METHACHOLINE)

$(CH_3)_3\text{-}N\text{-}CH_2\text{-}CH_2\text{-}O\text{-}C\text{-}NH_2$ ‖O

CARBAMYLCHOLINE (CARBACHOL)

$(CH_3)_3\text{-}N\text{-}CH_2\text{-}CH\text{-}CH_2\text{-}O\text{-}C\text{-}NH_2$ | CH₃ ‖O

CARBAMYL-BETA-METHYLCHOLINE (BETHNOCHOL)

$(CH_3)_3\text{-}N\text{-}CH\text{-}CH\text{-}CH_2\text{-}CH_3$ | CH OH

MUSCARINE

EDROPHONIUM (TENSILON)

PILOCARPINE

NEOSTIGMINE

$[(CH_3)_2\text{-}C\text{-}C\text{-}O]_2 = P\text{-}F$

DI-ISOPROPYL FLUROROPHOSPHATE (D F.P.)

$(C_2H_5\text{-}O)_2 = P\text{-}O\text{-}P = (\text{-}O\text{-}C_2H_5)_2$

TETRAETHY PYROPHOSPHATE (TEPP)

certain postganglionic sympathetic fibers (sweat glands), (d) at the myoneural junction of skeletal muscle, (e) in the motor cortex and (f) at synapses in the areas of the brain controlling autonomic activity(trophotropic centers) (Chap. 27). The response to acetyl choline at the autonomic ganglia and at the skeletal muscle endplate is similar to that pro-

duced by nicotine on these two structures. The action at these sites is often referred to as *nicotinic* because of this similarity of response. Nicotine acts in a biphasic manner. In small doses it causes stimulation; in large doses it depresses or paralyzes. Therefore, it produces a blocking effect at the ganglia and a curaremimetic effect at the motor endplate. At the *postganglionic cholinergic fibers* the behavior of acetyl choline differs from that at the ganglia and motor endplate. Instead it is similar to the response caused by the base muscarine. The action at this site, therefore, is often called *muscarinic*. Acetyl choline may thus be said to exert three distinct pharmacological effects—a muscarinic, a nicotinic and a curareform. These terms are poor ones but unfortunately are in general use in describing the action of autonomic drugs. A drug may manifest one, two or all three of the responses depending upon dose, pH and other factors.

INHIBITION OF ACETYL CHOLINE ACTION

Certain chemical substances may combine preferentially with the cholinergic receptors at the postganglionic fibers and thereby compete with liberated acetyl choline at these sites and prevent acetyl choline from acting. Such substances are referred to as parasympatholytic or anticholinergic. Atropine, hyoscyamine and scopolamine are substances which inhibit the action of acetyl choline upon the postganglionic cholinergic receptors. They, therefore, suppress parasympathetic activity. They neither inhibit the liberation of the acetyl choline nor do they decrease the activity of cholinesterases. These drugs are described further on.

PHARMACOLOGIC EFFECTS OF VARIATIONS OF STRUCTURE OF ACETYL CHOLINE

The molecule of acetyl choline may be considered as having three parts, (1) the quaternary ammonium group is at one end, (2) an acetyl group at the other and (3) the ethanol chain intervening between the two. The portion of the molecule bearing the quaternary ammonium group, as has been mentioned previously, is referred to as the *cationic head*. The cationic head and the acetyl group form bonds with the receptor sites on the effector cells. The configuration of the acetyl choline molecule may be altered by lenthening the chain, ethylation and so on. Such changes in structure cause considerable alterations in physiological activity. The evidence at hand indicates that simultaneous bonding of both heads of the choline-like substance is necessary at the receptor for activity and that the receptors to which the molecule becomes attached possess a specific type of molecular configuration. Thus, other quaternary bases may produce responses which are qualitatively similar to acetyl choline. The closer the structure is to acetyl choline the more nearly the action simulates that of acetyl choline. Variations in structure may be considered as being (a) at the cationic head, (b) the esteractic site and (c) in the aliphatic chain.

Variations at the Cationic Head

Optimal activity is obtained when the quaternary nitrogen is trimethylated. Some decrease in activity occurs if one ethyl group replaces a methyl. More than one ethyl group enhances blocking activity and increases the nicotinic and curareform type of response. Any atom which produces a quaternary basic ion (P, S, As, etc.) may be substituted for the nitrogen without marked decrease in activity. Converting the nitrogen atom from a quaternary to a tertiary one reduces all three types of activity.

Variations in the Ethanol Chain

Optimal activity is obtained when five atoms (excluding hydrogen) are present in the entire chain in a homologous series. In the choline series choline has four members while acetyl choline has five. Oxygen linkages of the ether type favor muscarinic activity while the carbonyl oxygen group favors nicotinic activity. Oxidation of choline to betaine reduces nicotinic activity and potency but retains muscarinic activity. Branching in the chain abolishes nicotinic effects and enhances the muscarinic. Acetyl beta methyl choline (Methacholine) Table I.22) and carbaminoyl beta methyl choline Bethanechol exemplify this alteration (Table I.22).

Changes at the Esteractic Site

Optimal muscarinic effects are obtained when choline is acetylated. The presence of the terminal hydroxyl group of choline usually decreases pharmacological activity. Esterification with acids other than acetic causes modifications in activity. Usually the potency is decreased. Esterification with an acid or conversion of the oxygen to an ether linkage enhances activity. Lenthening of the aliphatic chain in the esterifying (acyl) group increases nicotinic effects (Table I.22). Aryl (aromatic) substitution in the esterifying group further increases this trend. Thus, benzoylcholine, phenyl-acetylcholine and phenyl-propionylcholine manifest nicotinic activity only. Further aryl substitution of the acetyl residue produces a reversal of muscarinic effects and nullification of acetyl choline activity. In other words, the compound

becomes atropine-like in its behavior. *Esterification with the carbamino instead of the acetyl group causes an increase in nicotinic activity. This behavior is exemplified by carbonyl choline (Carbachol) (Table I.22). Alkyl substitution of the nitrogen atoms on the amino portion of the carbamino group produces compounds which antagonize choline, i.e. they are atropine-like. The dibutyl derivative of carbachol known as dibutoline exemplifies this behavior. Esterification of choline with dicarboxylic acids enhances nicotinic action and curareform activity and decreases muscarinic activity. This is exemplified by succinyl dicholine which is a depolarizing curaremimetic substance (Chap. 23). Converting choline to aromatic ethers, likewise, converts the compound to one which is curareform. Gallamine exemplifies this type of change.*

CHOLINE ESTERS

True cholinesterase is specific for acetyl choline and acetyl choline only. It has little or no influence on the hydrolysis of other esters of choline. Beta methylacetylcholine (Doriol or Mecholyl) is also hydrolyzed by true cholinesterase but it is slowly altered by the pseudo cholinesterases. This drug, therefore, causes sustained parasympathetic stimulation. Optimal activity of acetyl choline-like drugs is noted when the distance between the quaternary nitrogen atom and the carbonyl ($C=O$) group is 4.7 to 5.3 A°. This is probably the distance between the anionic and esteractic sites of acetyl choline and the receptor sites on true cholinesterase.

In summary then it appears that parasympathetic stimulation may be affected by (1) inhibiting the activity of cholinesterase, (2) increasing the production of acetyl choline or (3) administration of a drug with a muscarinic-like effect which is not easily destroyed by the tissues. Parasympathetic depression on the other hand is produced by decreasing (1) the amount of acetyl choline liberated, or (2) by increasing the rate of destruction of acetyl choline or (3) by interfering with the action of acetyl choline upon the end organs by the use of a substance which acts by competitive inhibition. Competitive inhibition is described in Chapter 24.

PARASYMPATHETIC STIMULATION DURING ANESTHESIA

Evidence of parasympathetic activity during anesthesia is abundant. Some of this stimulation is apparent; some is actual. Such manifestations of increased parasympathetic activity could result from (1) inhibition of cholinesterase activity, (2) increased acetylcholine production or (3) increased parasympathetic tone due to sympathetic inhibition. Cyclopropane, some barbiturates, particularly the thiobarbiturates, manifest increased parasympathetic activity. Ether and chloroform do not give this response. General anesthetics do not inhibit cholinesterase activity. The pseudo-cholinesterase activity of human serum is not inhibited by ether, chloroform, thiopental (Pentothal), cyclopropane, nitrous oxide or ethylene. High concentrations of local anesthetic drugs (procaine and tetracaine) do inhibit its action, somewhat like that of eserine. The amount of these drugs circulating in blood when they are used for local anesthesia is too small to be of significance.

Assay of Acetyl Choline

Blood pseudo-cholinesterase levels have become important to the anesthesi-

ologist particularly since the widespread adoption of succinyl choline as a muscle relaxant. The enzyme is formed in the liver. The enzymes may be assayed in blood by incubation of plasma or serum with acetyl choline in the chamber of the microspirometer of a Warburg or in the extraction chamber of the manometric apparatus of Van Slyke or Niell. Levels are low in innanition, liver insufficiency and chronic wasting diseases. The hydrolysis of the ester liberates acetic acid and choline. The acetic acid reacts with the plasma bicarbonates which liberates carbon dioxide. The rate of release is measured manometrically or volumetrically and curves are plotted graphically. The potency of cholinesterases in refrigerated blood preserved with citrate-citric acid-dextrose mixtures (ACD) remains unchanged over a three week period.

The detection and quantitative estimation of acetyl choline liberated at nerve endings in tissues and body fluids is difficult because the concentrations are infinitesimal and the hydrolysis occurs so rapidly. Concentrations of acetyl choline are so minute that they are expressed in gammas (1 gamma = 1/1000 of a mgm.). Biological methods of assay are generally used for quantitative estimation of the neurohormone. The body wall of the leech and the rectus abdominus of the frog, previously treated with eserine, contract when exposed to minute amounts of acetyl choline. Specimens of body fluid collected for assay of acetyl choline are preserved with eserine to inhibit hydrolysis of the ester.

Potassium ions potentiate the action of acetyl choline upon ganglionic cells. Thus, it is possible that changes in electrolyte concentrations could indirectly cause manifestations of stimulation.

Synthesis of acetyl choline from acetic acid and choline is aided by the enzyme acetylcholase. Energy is required for the synthesis. Presumably, in the brain at least, this energy comes from the breakdown of adenosine triphosphate. The synthesis of acetyl choline in the brain is inhibited in the presence of concentrations of narcotics that suppress respiration (Chap. 27). Quastel has shown, in vitro at least, that narcotics inhibit at links in the chain responsible for the oxidative synthesis of adenosine triphosphate. The formation of both the acetyl group and of adenosine triphosphate occurs during the oxidation of glucose. When the oxidative metabolism of glucose is depressed synthesis of both substances is depressed. Therefore, decreased formation of acetyl choline results concomitantly with suppressed oxidation. The effects of anesthetics upon the central control of parasympathetic activity is not known. It is known that acetyl choline is present in the brain in bound form. Anesthetics, notably ether, release the free acetyl choline from the bound form. Small quantities are liberated which could be responsible for the initial excitatory effects of narcotics.

ANTICHOLINERGIC (PARASYMPATHETIC DEPRESSANTS) DRUGS

Parasympathetic activity may be suppressed in one of two ways: (1) by using drugs which act competitively with acetyl choline at cholinergic postganglionic receptors or (2) by using drugs which inhibit the release of acetyl choline at these receptors. Compounds of the latter type are of little clinical importance at the present time. The competitive inhibitors, however, are used extensively in anesthesia for their para-

sympathetic depressant activity. These compounds are referred to as *parasympatholytic, cholinolytic,* or *anticholinergic drugs.* For many years atropine and its congeners have been used for this purpose and appear to remain the drugs of choice despite the numerous array of synthetic compounds which have recently been introduced to supplant them. The relationship of pharmacological activity to chemical structure of these compounds is not as readily apparent as it is with drugs acting at other sites. Generally, they resemble acetyl choline in structure (Table II.22). The molecule consists of three parts, as in acetyl choline—a nitrogen bearing portion which becomes attached to the cholinergic receptor, an intervening side chain and a carbonyl bearing portion. The alkyl and carbonyl bearing portions are pharmacologically inactive. There is much similarity between the anticholinergics and the local anesthetics (Chap. 21). Indeed, many anticholinergics possess varying degrees of local anesthetic activity. As is the case with local anesthetics, the nitrogen bearing portion is hydrophilic; the hydrocarbon residue is lipophilic. The intervening side chain has a sufficient number of carbon atoms so that its length is equal to the length of the chain in acetyl choline. It has been shown that aryl substitution of the carbonyl bearing end of the chain in acetyl choline nulifies cholinergic properties and converts the compound into one which is anticholinergic. The substitution of the two hydrogen atoms of carbamyl choline by phenyl radicals converts the compound to an anticholinergic derivative.

Anticholinergic compounds are either tertiary amines or quaternary bases. Atropine is a tertiary amine. However, it

TABLE II.22
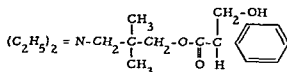
SYNTROPAN
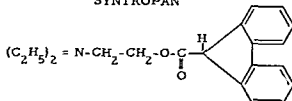
PAVATRINE
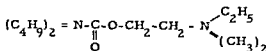
DIBUTOLINE
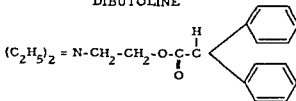
TRASENTINE

may be converted to a quaternary base and still retain its anticholinergic effects. Any alterations in pharmacological activity which occur are largely quantitative. The variations in activity of the numerous compounds which have been synthesized are noted primarily in the eye, where mydriasis occurs, in the heart where vagal blockade produces tachycardia, in the exocrine glands of the respiratory and gastrointestinal tract where secretions are decreased and in the visceral smooth muscle where decreased tone and motility result. Quaternization of the nitrogen atom increases basicity of the compound and makes it more alkaline. Local anesthetic activity is nullified and absorption from epithelial surfaces is decreased. The lipophilic or aromatic residue portion of the molecule is bulky. It is conceivable that the molecules orient themselves at the cell surface in the same manner as

local anesthetics do and that the activity at the cell surface is inhibited mechanically by the bulkiness or umbrella-like effect of the molecule.

Many of the synthetic anticholinergic drugs which have been recently introduced are patterned structurally after atropine or are compounds derived from atropine after degradation and removal of the non-essential parts of the molecule. Despite the numerous substances available as anticholinergics, atropine and alkaloids related to it continue to be the drugs of choice for this purpose in clinical medicine.

BELLADONNA ALKALOIDS

Chemical Nature

A group of plants belonging to the potato family known as *solanaceae* yield a group of chemically allied alkaloids which possess anticholinergic activity. The belladonna plant, or *Atropa belladonna*, known also as deadly nightshade, yields three important chemically and pharmacologically related alkaloids. The most important of these are *atropine*, *hyoscyamine*, and *scopolamine*. The alkaloids are found in the leaves and roots and in both the unripe and ripe fruit of the plant. The yield is approximately 0.5%. The thornapple, *Datura strammonium*, is also a source of these alkaloids. The proportion of atropine in it is less than in belladonna but the amounts of hyoscyamine are greater. Black henbane or *Hyoscyamus niger* also yields the alkaloid. These alkaloids are optically active. During the extraction of the alkaloid from the botanical source, hyoscyamine, which is a levorotatory compound, undergoes internal rearrangement and racemizes to atropine which is a mixture of the dextro and levo derivatives.

ATROPINE

Structure

Atropine is an ester, tropine tropate. Tropine is formed by the fusion of two rings, one five-carbon and one four-carbon fused so that two carbon atoms and the nitrogen atom are common to both rings. The nitrogen bears a methyl group, and, therefore, confers to the compound attributes of a tertiary amine. Tropine is both a *secondary alcohol* and a tertiary amine.

Optical Activity

The optical activity of these alkaloids is due to the tropic acid part of the molecule which possesses an asymmetric carbon atom. Tropine contains no asymmetric carbon atom and is, therefore, not optically active. Tropic acid is hydroxyphenylacrylic acid. The synthesis of atropine is of little interest in this discussion. Plants are still the source of these drugs. Tropine is chemically related to ecgonine, the alcohol portion of cocaine. Atropine possesses the following structure:
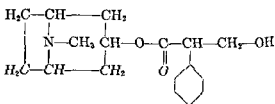
Properties

The free base consists of white, pointed, shiny needles which are quite insoluble in water (1 part in 600) and melt at 115°C. An aqueous solution of atropine (base) is alkaline to litmus, is bitter and unpleasant to taste. As is the case with other free alkaloid bases, it is soluble in organic solvents, such as chloroform (1 part in 3.5), in ether (1 in 50), but sparingly soluble in water. It is

soluble in alcohol and is volatile with steam.

When heated with alkali, such as barium hydroxide, atropine is hydrolyzed into the alcohol, tropine, and tropic acid. Esterification is accomplished by mixing equimolecular weights of both tropine and tropic acid and refluxing over a water bath with approximately twenty times their weight of hydrochloric acid for several hours. Fuming hydrochloric acid slowly hydrolyzes atropine at ordinary temperatures. The reaction is accelerated by heat.

Atropine heated in the presence of soda lime decomposes quickly into a variety of by-products among which is methyl amine. Aqueous solutions of atropine are stable but such solutions do not keep indefinitely. The tropic acid portion of the molecule loses a molecule of water to form tropine atropate or apoatropine when atropine is heated. Tropine and atropic acid result when apoatropine is hydrolyzed. The tropine does not undergo any change. Hyoscyamine, or levo tropine tropate, racemerizes into atropine when heated in the absence of air at 110°C. or if allowed to stand in an alcoholic alkaline solution for several hours. Neither atropine nor tropic acid possesses the physiological effects of the ester.

Salts

Atropine forms salts with mineral and organic acids. The most widely used salt is the sulphate. The salts are more soluble in water than the alkaloids. Atropine sulphate is a white, efflorescent, odorless, crystalline powder. One gram of atropine sulphate dissolves in 0.4 cc. of water, 0.5 cc. of glycerine, 3000 cc. of ether, and 450 cc. of chloroform at 20°C. The salts are less soluble in organic solvents than in water. Aqueous solutions of salts formed from strong mineral acids are neutral to litmus but acid to more sensitive indicators. The pure sulphate melts at 181°C. to 183°C.

Metabolism

The doses employed are small; therefore, the distribution and metabolism of atropine in the body is hard to follow. The drug disappears quickly from the blood. Atropine and hyoscyamine are eliminated partly unchanged in the urine of man after therapeutic doses. Approximately two thirds of a dose is destroyed in the body. The exact fate is not known but it appears that esterases in the liver hydrolyze atropine. The esterases are inhibited by anticholinesterases. Extracts of liver and mixtures of pancreatic enzymes hydrolyze the ester to tropic acid and tropine, but apparently intestinal and gastric juices do not. The drug resists putrefactive activity and may be recovered unchanged from specimens for toxicological study from cadavers. The drug may be recovered from brain, liver, kidney, spleen, or body fluids for toxicological analysis.

Detection: Biological Tests

Two types of tests may be used for the detection and quantitative estimation of atropine—chemical and biological. The biological are more sensitive. Minute amounts of the alkaloids produce specific and marked physiological responses on the eye and other parasympathetic innervated organs. Atropine causes a sustained dilatation of the pupil of the eye. The mydriatic action is usually observed in the cat's eye. Rate of dilatation and width of the pupil are the usual criteria employed. One drop of a 1 to 100,000 solution of atropine sulphate

produces appreciable mydriasis. The biological fluid to be examined is alkalinized and extracted with ether. The residue is dissolved in dilute sulphuric acid and instilled into one eye. The test is not specific for atropine because, unfortunately, cocaine, homatropine, hyoscyamine, epinephrine, and scopolamine produce similar responses and thereby limit the specificity of the test. Another biological test is based upon the inhibition of the vagal action of the frog's heart. The heart is first stopped by the action of a few drops of muscarine applied directly to the muscle. Muscarine is a vagal stimulant and stops the heart in diastole. The muscarine is removed by washing and a few drops of solution suspected of containing atropine are applied. The paralyzing action on the vagal endings restores the heart beat to normal if atropine is present.

Detection: Chemical Tests

Atropine responds to many of the general tests for alkaloids. These, however, are not specific for atropine. If any of the belladonna alkaloids (as little as .001 mgm.) are moistened with fuming nitric acid and evaporated to dryness, a transient violet color forms when the residue is treated with potassium hydroxide solution. This reaction is called Vitali's test. Atropine also responds to Gerrard's test. This test is performed by adding 1 ml. of a dilute atropine solution to 1 ml. of a 2% mercuric chloride dissolved in 50% alcohol. Reduction of the mercuric salt to the mercurous state results in a precipitation of the red oxide of mercury. The isomers of atropine and homatropine also give positive responses. An aqueous solution of hydrobromic acid and bromine, known as Wormley's reagent, produces a fine brown precipitate when added to solutions of atropine and its allies. Chlorauric acid forms precipitates with atropine, scopolamine, and hyoscyamine which may be used to differentiate one from the other. Atropine yields a dull brown precipitate which melts at 135° to 137°C. Hyoscyamine yields a yellow precipitate which melts at 160° to 162°C. Gravimetric methods must be employed to quantitatively measure the alkaloid in toxicological studies. This necessitates careful extraction of specimens. In recent years paper chromatography has been employed for detection of these and other alkaloids. These methods are too detailed for presentation here.

Tincture of Belladonna

The tincture of belladonna is an alcoholic solution prepared by steeping the leaves of belladonna in water. It contains 27 to 33 mgm. of total miscellaneous alkaloids per 100 ml. of fluid in addition to inert substances and other extractives occurring in the leaves of the plant. The alkaloid content varies because of the diversity of the sources of the leaves. The *fluid extract of belladonna*, which is little used, shows on assay 0.4 mm. mgm. per 100 ml. of fluid. The sulphate and the free base, as well as the tincture, are included in the U.S.P.

SCOPOLAMINE

Source

Scopolamine (also called hyoscine) is also found in varying quantities in the Solanaceae, which are the sources of atropine and hyoscyamine. The chief source, however, is from the *Scopola Japonica* which is native to Germany, Russia and Hungary. The alkaloid was first isolated by E. Schmidt (1888). The free alkaloid (basic form) is a syrupy, white liquid which crystallizes from ether into a white powder which melts

at 39°C. This powder absorbs moisture from air and is again converted to a syrup. Aqueous solutions of scopolamine base are alkaline. The drug is a weaker base than atropine. Scopolamine forms salts with mineral and organic acids. The hydrochlorides and sulphates are known but the *hydrobromide is soluble, stable and, therefore, the most commonly employed salt.*

Structure

Scopolamine is the tropic acid ester of *scopine,* or, more accurately, *scopine tropate.* The ester, as is the case with atropine, is readily hydrolyzed. Scopine and tropic acid form if a mild agent, such as pancreatic lipase, is employed. Scopine differs from tropine in that an *epoxy,* or ether type, linkage is interposed in the five-carbon ring (between carbon 8 and 7) as shown in the following structure:
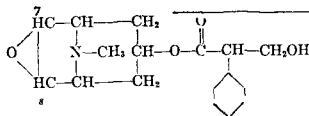
Hydrolysis by means of a strong base, such as barium hydroxide converts scopine to *scopoline* (or oscine). An internal rearrangement occurs with the conversion of the epoxy bridge to a hydroxyl group. Before the structure of scopolamine was precisely established the drug was believed to be scopoline tropate.

Optical Activity

Scopolamine is optically active. Both the alkaloid as well as the salts are levorotatory. The optical activity is due to the asymmetric carbon atom in tropic acid and not to any grouping in the scopine part of the molecule. The rotation of the free alkaloids is

$$[\alpha]_D^{25°} -28°.$$

Dextro scopine tropate is not a naturally occurring compound. A racemic mixture may be formed known as *atrascine* which bears the same relationship to scopolamine as atropine does to hyoscyamine. Racemization occurs when an alcoholic solution of scopolamine is allowed to react with potassium hydroxide.

Salts

Scopolamine hydrobromide is a colorless, odorless, white powder with a bitter taste. It is soluble in water (1 part in 1.5), alcohol (1 in 20), and chloroform, but only slightly so in ether. The salt is stable. Its solution may be heated and stored indefinitely in sterilized ampules. Solutions of the hydrobromide are neutral to litmus but acid to more sensitive indicators. Scopolamine is stabilized with 10% mannite, a hexose. Scopolamine is readily absorbed if administered orally. Distribution and destruction in the tissues is similar to that of atropine. Less than 1% of the drug is eliminated unchanged into the urine. The drug undergoes hydrolysis as do other tropic acid esters. The salt melts at 190° to 192°C. Its optical rotation is

$$[\alpha]_D^{25°} -24 \text{ to} -26°.$$

Identification

Scopolamine responds to many of the tests of and gives reactions similar to

other belladonna alkaloids. A minute amount treated with concentrated nitric acid followed by saturated potassium hydroxide produces a violet color. Precipitates form with alkaloidal reagents. Chlorauric acid added to aqueous solutions of scopolamine base or its salts yields a brown precipitate which melts at 210° to 214°C. Scopolamine does not form a precipitate with mercuric chloride (1% in 10% alcohol) in contradistinction to atropine which does. As is the case with atropine and its isomers, scopolamine may be detected by biological tests, since scopolamine is both a mydriatic and vagal depressant.

SYNTHETIC SUBSTITUTES FOR ATROPINE

The first synthetic substitute for atropine was homatropine, which was introduced by Ludenburg in 1880. Since that time many substances resembling atropine have been synthesized and tested pharmacologically and clinically. Few are superior to the belladonna alkaloids for the relief of gastro-intestinal spasm or for mydriasis. As far as the vagal blocking and antisecretory effects during anesthesia are concerned, none is superior to or has any distinct advantage over the belladonna alkaloids. At first the substitutions were modifications of the atropine molecule, as for example homatropine, which retained the tropine portion of the molecule or apoatropine (syntropan) which retained the tropic acid portion. Gradually the number of drugs available has multiplied so that today they form a heterogenous group, the systematic classification of which is beyond the scope of this book. Some are quaternary derivatives of the natural alkaloids while others are synthetic esters which have no resemblance what-

TABLE III.22

$$CH_3\text{-}(CH_2)_4\text{-}\underset{\displaystyle CH_3}{\overset{\displaystyle |}{CH}}\text{-}NH_2$$
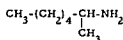
TUAMINOHEPTANE (TUAMINE)

$$CH_3\text{-}(CH_2)_4\text{-}\underset{\displaystyle \underset{\displaystyle CH_3}{\overset{\displaystyle |}{N\text{-}H}}}{\overset{\displaystyle |}{CH\text{-}CH_3}}$$

2, METHYL AMINO HEPTANE (OENETYL)

$$CH_3\text{-}CH_2\text{-}\underset{\displaystyle CH_3}{\overset{\displaystyle |}{CH}}\text{-}CH_2\text{-}\underset{\displaystyle CH_3}{\overset{\displaystyle |}{CH}}\text{-}NH_2$$
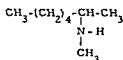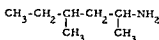
METHYL HEXANE AMINE (FORTHANE)

ever to the tropines except that a general configuration consisting of a lipophilic grouping, a hydrocarbon residue separated by an intervening carbon chain appears to predominate in most compounds (Table I.22). The derivatives of atropine and scopolamine will be described briefly, however. For data on the newer synthetic anticholinergics, the reader is referred to more detailed texts.

HOMATROPINE

Homatropine is a synthetic substitute for atropine prepared by esterifying tropine with *mandelic acid*. Mandelic acid is phenylhydroxyacetic acid. It differs from tropic acid in that it contains one *carbon atom less. The phenyl and hydroxyl group* are both on one carbon. It is, therefore, the lower homologue. Synthetic atropine-like drugs are often referred to as *tropeines*. Homatropine possesses physical and chemical properties similar to those of the naturally-occurring allies.

Properties

The base is a white, crystalline substance, slightly soluble in water, soluble in alcohol, chloroform, ether and other

organic solvents. It melts at 99° to 100°C. Salts form of which the most widely employed is the hydrobromide, a white crystalline powder. Homatropine hydrobromide melts at 212°C. with partial decomposition. The salts are more soluble in water than the free base. A salt forms with chlorauric acid ($AuCl_3 \cdot HCl\ 4H_2O$) which melts at 142° to 145°C. The melting point differs and, therefore, distinguishes the salt from atropine. Homatropine does not respond to the Vitali test or to the nitric acid test, thus further distinguishing it from the other three alkaloids. Mandelic acid possesses no asymmetric carbon; neither does tropeine. Therefore, these substances are not optically active.

OTHER HOMATROPINE DERIVATIVES

Homatropine reacts with methyl bromide to form homatropine methyl bromine or novatrine. The methyl group becomes attached to the tertiary amino nitrogen which is then converted to the quaternary base. A methyl nitrate is also known which is similar pharmacologically to homatropine.

DERIVATIVES OF SCOPOLAMINE

The tertiary nitrogen atom of scopolamine may be quaternized by treating it with methyl bromide to form *scopolamine methyl bromide* (Pamine). The compound then has two methyl groups on the nitrogen atom, as well as a bromide radical. This alteration in molecular structure nullifies the central action of scopolamine but enhances its spasmolytic action on visceral smooth muscle and prolongs its action somewhat. An N-oxide may be prepared known as *geno-scopolamine*. The oxygen atom is attached to the tertiary nitrogen. This substance is less toxic

and less potent than scopolamine. It is now considered obsolete.

SYMPATHOMIMETIC COMPOUNDS

Adrenergic Activity

Substances which evoke responses similar to those produced by stimulating the sympathetic division of the autonomic nervous system are referred to as sympathomimetic compounds. The responses are similar to those produced by the sympathetic (adrenergic) nerves; therefore, they are called *sympathomimetic* or *adrenergic agents*. Most adrenergic drugs are related to beta phenyl ethylamine

$$\langle\!\!\!\!\bigcirc\!\!\!\!\rangle\!-\!CH_2\!-\!CH_2\!-\!NH_2.$$
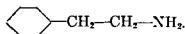
Epinephrine and norepinephrine are the prototypes of several hundred chemically and pharmacologically related amines of which several dozen are in clinical use.

The transmission of impulses in the sympathetic division of the autonomic nervous system is mediated, as in the parasympathetic division, by humoral mechanisms. Epinephrine and norepinephrine are intimately concerned with this neuroeffector transmission. A clear-cut parallelism cannot be drawn between the effects of acetylcholine on the cholinergic receptors and those of adrenergic substances on their effector cells. Likewise, parallelism cannot be drawn between cholinesterase and its inhibitors and enzymes which destroy adrenergic substances. Nor can parallelism be drawn between adrenergic and cholinergic blocking agents. Epinephrine and other adrenergic substances act at a specialized receptor mechanism known as the *adrenergic* or *adrenotropic* receptor. The exact nature of the adrenergic

receptor is not known and how the adrenergic substances react with the receptor likewise is not known. Some of the receptor cells which respond to adrenergic agents are stimulated by epinephrine while others are inhibited. Agents capable of blocking adrenergic activity are available. Some of the actions of epinephrine may be blocked by these agents while others may not be. The existence of two principal types of receptors has been postulated—an alpha and a beta. The *alpha* receptor is concerned with *excitatory* responses and is blocked as a rule by adrenergic blocking agents. The *beta* is concerned with *inhibitory* responses and is not blocked by antiadrenergic agents. Modificaton of the epinephrine molecule results in compounds which have greater or less effects than epinephrine on adrenergic receptors. Definite relationships of chemical structure to pharmacological activity can be demonstrated in these various compounds.

CHARACTERISTICS OF SYMPATHOMIMETIC COMPOUNDS

Sympathomimetic compounds cause varying degrees of myocardial stimulation, central nervous system stimulation, local anesthetic effects, glycogenolysis, inhibition of visceral smooth muscle, bronchial dilatation and so on. Most sympathomimetic compounds raise blood pressure and are, therefore, referred to as pressor drugs, vasoconstrictors or vasopressors. The pressor effect, however, is not necessarily a neurohumoral effect, but may instead be a neuromuscular effect. Some compounds are inhibitors and act as vasodilators. The term vasopressor is not a desirable one for these substances.

Aliphatic Amines

Although sympathomimetic activity is not necessarily an attribute of any one particular chemical configuration the majority of useful compounds are amines of various types (Tables III.22; IV.22; V.22). The compounds with the simplest structure are *aliphatic* or straight chain amines. Pressor activity in straight chain compounds becomes apparent when four carbon atoms are reached. Compounds with less than four carbon atoms are not sympathomimetic. Activity becomes maximal at six carbons and gradually decreases as the chain lengthens. Compounds in which the amino group is attached to the second (2-amino) carbon atom are more potent and longer acting than those in which it appears on the first carbon atom. The clinically useful aliphatic amines are of the 2-amino type. Branching of the aliphatic chain produces variable effects on pressor and myocardial stimulating activity. Unsaturated linkages in the chain diminish the pressor activity. The best known compounds of this aliphatic type are 2-methyl-amino-heptane (Oenethyl) and Octin (Table III.22).

Cyclic Compounds

The number of useful aliphatic amines is obviously limited. Few are useful clinically (Table III.22). Replacement of a hydrogen atom on an aliphatic chain by a cyclic structure increases the number of possible amines manyfold. The cyclic structure may be an alicyclic, aromatic or heterocyclic nucleus. Thus, four types of sympathomimetic derivatives may be recognized, the *straight chain,* the *alicyclic,* the *aromatic* and the *heterocyclic.* Usually only one cyclic nucleus is found. Compounds with more than one cyclic nucleus are clinically unimportant as vasopressors. The cyclic nuclei usually are five or six membered

TABLE IV.22

β α
CH$_2$-CH$_2$-NH$_2$
PHENYLETHYLAMINE

CHCH$_2$NH$_2$
OH
PHENYLETHANOLAMINE

CH$_2$-CH NH$_2$
CH$_3$
AMPHETAMINE
(BENZEDRINE)

CH$_2$-CH NH-CH$_3$
CH$_3$
METHAMPHETAMINE
(DESOXYEPHEDRINE)

CH$_3$
CH$_2$-C-NHCH$_3$
CH$_3$
MEPHENTERMINE
(WYAMINE)

CH-CH NH$_2$
OH CH$_3$
PHENYL PROPANOLAMINE
(PROPADRINE)

CH-CH NH-CH$_3$
OH CH$_3$
EPHEDRINE

CH-CH$_2$-NH-CH$_3$
CH$_3$
PHENYL PROPYL METHYLAMINE
(VONEDRINE)

CH$_2$-CH-NH-CH$_3$
OCH$_3$ CH$_3$
METHOXY PHENAMINE
(ORTHOXINE)

OCH$_3$
CH-CHNH$_2$
CH$_3$O OH CH$_3$
METHOXAMINE (VASOXYL)

HO CH$_2$-CH$_2$-NH$_2$
TYRAMINE

HO CH-CH$_2$-NH-CH$_3$
OH
SYNEPHRINE

HO
CH-CH$_2$-NH-CH$_3$
OH
PHENYLEPHRINE
(NEO SYNEPHRINE)

HO
HO CH-CH$_2$-NH$_2$
OH
NOREPINEPHRINE

HO
HO CH-CH$_2$-NHCH$_3$
OH
EPINEPHRINE

HO
HO CH-CH$_2$-NH CH=(CH$_3$)$_2$
OH
ISO PROTERENOL (ISUPREL)

HO CH$_2$-CH$_2$ NHCH$_3$
EPININE

HO CH$_2$-CH-NH$_2$
CH$_3$
HYDROXYAMPHETAMINE
(PAREDRINE)

HO CH$_2$-CH-NHCH$_3$
CH$_3$
PAREDRINOL

OH
OH CH - CH - CH$_3$
OH NH$_2$
CO
NORFEDRIN
(CORBASIL, COBEFRINE)

HO CH - CH - NH$_2$
OH CH$_3$
METARAMINOL
(ARAMINE)

TABLE V.22
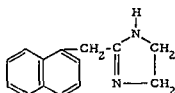
NAPHAZOLINE (PRIVINE)
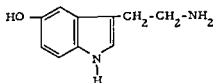
5 - HYDROXYTRYPAMINE
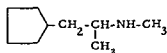
CYCLOPENTAMINE (CLOPANE)
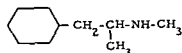
PROPYLHEXEDRINE (BENZEDREX)

rings. Actually the cyclic compounds are mixed, that is, they are composed of a ring and an aliphatic chain. The carbon chain in these is shorter than in the purely straight chain compounds. Usually, optimal pressor activity results when the chain has two carbons. Pressor activity decreases when four carbon atoms are reached. The amino group may be either on the chain or on the ring. Substitution of radicals on the ring, in addition to substitutions on the amino group, results in more potent vasopressors than is noted in compounds which

are purely aliphatic straight chain derivatives. Optimal pressor activity occurs when the amino group is on the second carbon atom, that is, when the distance between the amino group and the ring is 2 carbon atoms. The cyclic structure may be alicyclic or aromatic. There is little difference in potency between the 5 membered (cyclopentyl) and the 6 membered (cyclohexyl) derivatives. In other words, the addition of one more carbon atom to the ring has little effect on potency. Unsaturated linkages in an alicyclic ring, likewise, cause no notable effects in potency. Variations in ring structure from the saturated cyclohexane to the unsaturated aromatic ring produce compounds of like potency. Alicyclic compounds possess greater central stimulating action and less cardiac stimulating effects than the straight or branched chain derivatives.

Aromatic Amines

The better known of the pressor substances are aromatic compounds (Table IV.22). By this is meant that, they are compounds having a benzene ring or other aromatic nucleus substituted on the straight chain derivatives. The substitution of an aromatic nucleus on an aliphatic amine does not necessarily increase sympathomimetic activity. Central stimulating activity appears to increase as a ring tends to become aromatic. Certain aromatic amines have only slightly greater pressor activity than corresponding alicyclic or aliphatic derivatives. Variations in pressor activity appear to be more of a function of substituents on the aromatic nucleus than that of the ring itself. Although the most important aromatic derivatives contain the benzene ring, other aromatic nuclei may be used to form these drugs. For example, the alpha

naphthalene nucleus, the benzopyrene ring, which is found in naphazoline, or an indol nucleus may appear instead of the benzene ring. The amino group is usually separated from the aromatic nucleus by several carbon atoms. Irrespective of the type ring which appears, the nature of the substituents on the ring, or the types of radicals on the nitrogen atom, maximal sympathetic activity is obtained when two carbon atoms separate the ring from the amino group. This applies to all the actions of a compound be the action excitatory, inhibitory, cardiac stimulating or pressor. Lengthening the side chain to four or five carbon atoms not only results in an almost complete disappearance of pressor activity, but also causes a considerable increase in toxicity. Conversion of the aromatic nucleus to an alicyclic one by hydrogenation appears to alter the potency only slightly. Phenylethylamine, for example, has the same pressor activity as cyclohexyl ethylamine. Phenyl ethylamine is the basic structure around which aromatic amines are built. Lengthening the chain of this amine to more than two carbon atoms reduces its pressor activity.

Substitution on the Aliphatic Chain— Aliphatic Substituents

Substituents on the straight chain and on the amino group alter the pharmacologic effects also. Most compounds in current use have a hydroxyl or a methyl group on either the alpha or beta carbon atom of the aliphatic chain. Placing a methyl group on the beta carbon causes a decrease in adrenergic activity. Phenylisopropyl methylamine contains a beta methyl group which apparently weakens its cardiovascular and central stimulating effect but causes it to retain its local vasoconstrictor activity. When the methyl group is substituted on the alpha carbon in an aromatic amine with two carbon chains the pressor activity and the smooth muscle stimulating properties are usually enhanced, although it is possible for them to be decreased or unchanged.

Alpha Methyl Substituents

Compounds which contain a methyl group on the alpha carbon are sometimes referred to as the *ephedrine type* (Table IV.22). They are less potent in regards to pressor activity, more toxic, more stable and longer lasting. They may be taken orally and are not detoxified by enzymes which affect epinephrine. Amphetamine which has a methyl group on the alpha carbon is equally as potent as phenyl ethylamine in regards to pressor activity. On the other hand, *cobefrin* which differs from epinephrine in having a methyl group on the alpha carbon is ¼ as potent. Alpha methyl substitutions cause an increase in central excitatory activity, glycogenolytic activity and pressor effects. Replacement of the methyl group by an ethyl group nullifies activity.

Hydroxy Substituents

Compounds with a hydroxyl group on the beta carbon, that is, on the carbon carrying the aromatic nucleus are also known (Table IV.22). Alpha hydroxy substituents are unimportant. The hydroxyl group in the beta position alters pressor activity very little but enhances the cardiac stimulating action and the inhibitory effect on smooth muscle. The glycogenolytic effect and central stimulating effect presumably are reduced by this substitution. Ephedrine has a hy-

droxyl group on the beta or aromatic carrying carbon atom.

Substitution on the Aromatic Nucleus

The presence of a hydroxyl group on an aromatic nucleus converts a compound into an aromatic alcohol or phenol (Table IV.22). Sympathomimetic activity is enhanced by this substitution. Sympathomimetic potency of aromatic amines varies with the number and the position of hydroxyl groups on the ring. As a rule, sympathomimetic activity is increased and the central stimulating action is decreased by the hydroxy substitution. The stability of the compound also is decreased. Such compounds are easily oxidized to form dark brown substances known as quinones. They are subject to enzymatic changes in the body. Substitution of a hydroxyl group in the para position increases pressor activity slightly but enhances inhibitory or smooth muscle activity. *Synephrine* which consists of a two carbon methylated amine results when the molecule has such a configuration. A single hydroxyl group in the meta position results in *phenylephrine* (Neosynephrine). This has a greater pressor effect than synephrine. Compounds with a single hydroxyl group on the benzene ring manifest greater pressor activity than those without hydroxyl groups. Thus ephedrine which has no hydroxyl group on the aromatic nucleus is less effective than *phenylephrine* (Neosynephrine) or synephrine each of which has one. The para-hydroxy and the meta-hydroxy derivatives are more potent than the ortho. The presence of a hydroxyl group on the beta carbon in addition to one or more hydroxyl groups on the aromatic nucleus confers additional sympathomimetic activity to the compound. The hydroxyl group in the ortho position enhances the pressor effects to a greater extent than the cardiac effects. Phenylephrine (Neosynephrine) elevates the blood pressure by its pressor effect rather than by its cardiac accelerating or stimulating effect. The two hydroxyl groups in epinephrine are in the meta and para positions respectively. Such an arrangement of hydroxyl groups on the aromatic nucleus is referred to as the *catechol* nucleus. Central effects and duration of action are greatly diminished by the presence of hydroxyl groups on the aromatic nucleus. Groups other than the hydroxyl, such as the amino, nitro, halo, alkyl, alkoxy and so on may be substituted on an aromatic nucleus. Physiological activity is usually decreased by such substitutions and is less than that of the hydroxy counterparts. A reversal of the effect on smooth muscle occurs as larger substituents appear on the aromatic nucleus. The diethoxy derivative of propadrine is a bronchodilator.

Amino Substitutions

The alkyl substitution of the hydrogens of the amino nitrogen alters the physiological and chemical activity of the compound. The compound is no longer a primary amine, but becomes either a secondary or tertiary amine, depending upon hydrogens replaced. The physiological alteration depends upon the size and the number of the alkyl groups on the nitrogen atom. Methylation of the nitrogen atom does not affect the pressor response but the smooth muscle, inhibitory and blood sugar elevating properties are enhanced. Epinephrine and norepinephrine are identical in structure save for the fact that the amino nitrogen in epinephrine

is methylated. The prefix *nor* before the name of a compound indicates that a methyl group which is normally present in that compound has been removed. The addition of the methyl group to norepinephrine alters its pharmacological activity and increases its cardiotonic effects. Replacement of both hydrogen atoms by two methyl groups on the amino nitrogen, as a rule, reduces sympathomimetic activity. Increasing the size of the substituting group decreases the pressor activity but increases the bronchodilator, cardioaccelerator and central excitatory activity. Converting the amino nitrogen to a quaternary ammonium base imparts a nicotine-like activity to the compound and nullifies the *sympathomimetic activity*.

Effect on Cardiac Irritability

Sympathomimetic amines may increase cardiac irritability. This irritability may be further enhanced when such compounds are used in conjunction with alicyclic and halogenated hydrocarbons. Severe cardiac arrhythmias, such as ventricular tachycardia or fibrillation have occurred when certain pressor amines have been used in conjunction with cyclopropane, cyclobutane, chloroform, ethyl chloride, trichlorethylene, halothane (Fluothane) and other halogenated hydrocarbons. The sympathomimetic amines which consistently produce ventricular arrhythmias when used in combination with cyclopropane are primary and secondary amines having a catechol nucleus. Both epinephrine and norepinephrine, which is a secondary amine with a catechol nucleus and norepinephrine, which is a primary one produce this effect. Phenylephrine (Neosynephrine) is a secondary amine but it is not a catechol amine because it has only one hydroxyl on the aromatic ring. It does not produce arrhythmias with the aforementioned anesthetics. *Sympathomimetic substances of the tertiary amino type which have a catechol nucleus and primary amines are usually inactive in this respect.* Ephedrine is a secondary amine with no catechol nucleus and, therefore, does not increase cardiac irritability with these anesthetics.

Optical Activity

Many aliphatic and aromatic sympathomimetic amines have one or more asymmetric carbon atoms and are, therefore, optically active. Ephedrine, epinephrine and norepinephrine and amphetamine and many others are optically active. Ephedrine, for example, has two asymmetric carbon atoms and, therefore, forms four optical isomers. The naturally occurring substances, such as epinephrine and norepinephrine, are levorotatory. The levorotatory optical isomers are more active physiologically than the dextrorotatory or the racemic. Levo-epinephrine is approximately twenty times more active than the dextro. Racemic ephedrine is less active than the levo.

Basicity and Salt Formation

Sympathomimetic amines are bases and, therefore, form salts with acids. The bases are less soluble in water than in salts. In addition they are lipophilic and penetrate into nervous tissues. Some are sufficiently volatile so that they may be inhaled to produce vasoconstriction of the nasal mucous membranes.

EPINEPHRINE AND NOREPINEPHRINE

Epinephrine and norepinephrine are not only closely related chemically and pharmacologically but they are also

found together in the medulla of the adrenal gland. For this reason both substances are discussed simultaneously. Norepinephrine is epinephrine minus the methyl group on the nitrogen atom. Both are catechol amines. Epinephrine is 3,4 dihydroxyphenylethanol methyl amine while norepinephrine is 3,4 dihydroxyphenylethanolamine. In both animals and man the proportion of epinephrine in the adrenal gland is 85% to 15% norepinephrine. Norepinephrine is found in almost pure form at the ends of adrenergic nerves and in the structures innervated by these nerves. In certain abnormal conditions, notably pheochromocytoma (an adrenal tumor) norepinephrine may be 90% of the mixture. Both derivatives are optically active. Levoepinephrine is 20 times more active physiologically than the dextro. Levonorepinephrine is approximately 45 times more active than the dextro. The generic name for norepinephrine is *levoarterenol*. However, it appears that most workers prefer to refer to the compound as norepinephrine. This name appears to be more prevalent. The racemic form of norepinephrine has been known for approximately 50 years. Clinical interest did not develop in the compound until it was prepared in its levo form. It was used clinically in the early 1950's. The fact that epinephrine from glandular sources is a mixture of both epinephrine and norepinephrine remained undiscovered for some time due to the difficulties in the methods of analysis. Both compounds respond to the same general tests and are difficult to distinguish from one another.

History

In 1856, Colin and Vulpian demonstrated that a solution of ferric chloride produced a blue color at the medullary portion when applied to the cut surface of the adrenal gland. Phenols as a class react in this manner with ferric chloride. This response was obtained because the drug is a phenol. A similar coloration was also obtained when blood from the adrenal vein was treated similarly. This work represented the first step in the isolation of the hormone and suggested, as was later proved, that the substance is elaborated in the medulla of the adrenal gland.

Oliver and Shaefer (1895) first demonstrated the sympathetic stimulating effects of extracts of the adrenal medulla upon the cardiovascular system. Abel and Crawford (1897) first isolated the hormone from the gland. Takamine (1901) prepared crystalline epinephrine in pure form. Jowet (1904) first described its molecular structure. Stolz (1905) first synthesized epinephrine.

Source

Both substances are elaborated from the amino acid, phenylalanine and tyrosine, to which they are allied chemically. The exact manner in which the acid is converted to these derivatives is not known. Presumably phenylalanine is first converted to hydroxy phenylalanine (tyrosine) and then to dihydroxyphenyl alanine (a substance known as DOPA). Decarboxylation converts this to dihydroxyphenyl ethylamine (hydroxytyramine) which is then hydroxylated at the beta carbon to norepinephrine. It is believed that in the body norepinephrine can be converted to epinephrine by a methylation reaction involving enzymes of the adrenal (page 459).

Epinephrine may be prepared from glands of slaughtered animals by maceration and extraction with dilute alcohol.

⬡—CH₂—C—COOH with H above and NH₂ below

$$\text{⬡—CH}_2\text{—}\underset{\text{NH}_2}{\overset{\text{H}}{\text{C}}}\text{—COOH}$$

→ OH⬡—CH₂—C—COOH (H above C, NH₂ below)

→ OH⬡—CH₂—C—COOH (H above C, NH₂ below; OH on ring)

→ OH⬡—CH₂—CH₂—NH₂ (OH on ring)

→ OH⬡—CH₂·—CH₂—NH₂ (OH on ring and OH below CH)
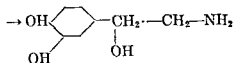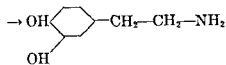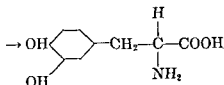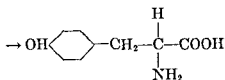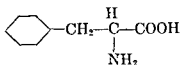
The extraction is carried out under oil to exclude air which would otherwise oxidize the hormones. The extract is concentrated in a vacuum after which the proteins are precipitated by heat. The crude product is purified by crystallization with alcohol and ether. Epinephrine and norepinephrine from all mammalian sources are identical chemically. Commercial epinephrine obtained by extraction of the adrenal gland contains up to 18% norepinephrine. The presence of the norepinephrine apparently has no significant effect on the pharmacologic properties of epinephrine. For many years the contamination of epinephrine by norepinephrine remained unrecognized due to inadequacies of methods of distinguishing the two. Pure epinephrine and norepinephrine may be prepared synthetically from catechol. In the synthesis of epinephrine catechol monochloracetyl chloride is treated with methyl amine (Stolz-Flaescher synthe-

sis). The resulting racemic mixtures are resolved into the dextro and levo components.

Properties

Both epinephrine and norepinephrine exhibit properties characteristic of phenols and amines. The amino portion confers basicity to the compound so that it forms salts with mineral and organic acids. The naturally-occurring drugs are levorotatory. The synthetic product is racemic. The levo isomer is about 20 times more active physiologically than the dextro. The racemic form which is an equimolecular mixture of the two optical isomers, is only one-half as active as the levo.

Both epinephrine and norepinephrine are unstable due to the presence of the two readily oxidizable phenolic hydroxyl groups on the aromatic ring structure. Compounds of similar structure minus the hydroxyl group (ephedrine) are more stable. Epinephrine is very rapidly oxidized in air, in alkaline solutions, by aldehydes, and by various oxidizing agents, even weak ones.

Metabolism and Elimination

The fate of epinephrine and norepinephrine in animal tissues is a subject of intense interest because both compounds are associated with mediation of sympathetic nervous impulses. The situation is not parallel to the one found at cholinergic nerve endings in which the mediator, acetylcholine, is rapidly hydrolyzed by cholinesterase. Epinephrine may be inactivated by at least three mechanisms: (1) Oxidative deaminization, (2) oxidation of the phenolic hydroxyl groups, and (3) by conjugation of the phenolic groups with glucuronic or sulphuric acid.

Oxidative deaminization is facilitated by the enzyme *amine oxidase*. This enzyme is not specific for epinephrine since in vitro it oxidizes many other primary, secondary and tertiary amines, such as phenyl ethylamine, tyramine and phenolic derivatives of these. The end products of oxidation are an aldehyde and ammonia which in turn are converted to a carboxyl derivative and urea. In vitro both epinephrine and norepinephrine are oxidized by amine oxidase. Norepinephrine is oxidized somewhat more rapidly. It has not been conclusively established that amine oxidase is the principal enzyme inactivating epinephrine and norepinephrine in vivo. Ephedrine is resistant to oxidation by the enzyme. In addition it inhibits the action of the amine oxidase upon epinephrine in vitro. Gaddum and his co-workers introduced the concept that ephedrine acts by prolonging the action of epinephrine or other adrenergic mediators in a fashion paralleling those of cholinesterase inhibitors upon acetylcholine. This concept, though accepted by many, has little valid proof to substantiate it. Cocaine also inhibits amine oxidase in vivo. Amine oxidase is concentrated to the greatest extent in the liver.

Adrenochrome

Oxidation of the phenolic hydroxyl groups results in brown products known as quinones. Two atoms of hydrogen are lost to form an ortho quinone derivative. This compound undergoes further change to a red-colored indole derivative called *adrenochrome*. Adrenochrome is physiologically inactive. It polymerizes to brown melanin pigments. This type of oxidation occurs spontaneously in aqueous solutions of epinephrine and other

amines, which have hydroxyl groups on the aromatic nucleus.

The catechol and phenolic amines are conjugated in the liver and intestine with sulphuric or glycuronic acid. After oral administration of epinephrine the conjugated products are found in the urine along with traces of free epinephrine. The inactivation for these esterases probably accounts for the inactivity of this type of compound after oral administration. The rate of inactivation and duration of action of epinephrine and norepinephrine varies with the route of administration. When introduced directly into the circulating blood inactivation is rapid. In the peripheral areas these substances may be trapped in the tissues by their own vasoconstrictor effects and produce a longer effect. At present the principal in vivo mode of inactivation has not been established.

Tissue Epinephrine Concentrations

The qualitative detection and quantitative estimation of epinephrine ha been, for years, difficult to accomplish Methods of assay have been biologica and chemical. Chemical methods hav been largely colorimetric. A mass o data has accumulated in the literatur concerning tissue and plasma concen tration which does little except creat confusion. The factors which have con tributed to the difficulties are as follows (1) The concentrations circulating ir plasma are minute. Methods of detectior have not been sufficiently sensitive. (2 Methods of detection have not been specific for epinephrine but respond to cate chol amines or monophenolic amines (3) Separation from protein-containing tissues result in low yields because the amines are either destroyed or adsorbed

to protein. (4) The circulating amines are not necessarily a reflection of the quantities released from their sources or the amount present at receptors due to this rapid destruction.

Much of the data in the older reports has been obtained by methods of bioassay. In these the pressor action of the drug on the mammalian vascular system is noted by adding the drug to be tested to smooth muscle strips innervated by sympathetic fibers and observing the contractility. Obviously these methods have little application to anesthesia research. Various colorimetric and fluorometric tests have been utilized. Recently the trihydroxyindole method has been introduced which is specific for and permits the differentiation of epinephrine from norepinephrine. These data obtained using this method indicate that the plasma epinephrine levels vary between 1 to 2 micrograms and that norepinephrine levels range from 4 to 5 micrograms per liter. Epinephrine is released continuously and not merely at times of stress as postulated by Cannon, provided the innervation of the gland remains intact. The rate of utilization of epinephrine has been estimated to be 0.033 micrograms per liter per minute. Changes in plasma level occur rapidly. The adrenal gland does not appear to be the source of the major portion of the norepinephrine. Presumably it arises from adrenergic innervated structures.

ANESTHESIA AND THE SYMPATHETIC NERVOUS SYSTEM

For many years the behavior of the sympathetic nervous system during anesthesia has been a subject of considerable interest. Ether, chloroform, vinyl ether and other anesthetics have been referred to as being sympathomimetic. The evidence for this has been both indirect and direct. There is considerable data which indicates that during anesthesia epinephrine and norepinephrine are liberated from the adrenal glands, the sympathetic nervous endings and perhaps also within the central nervous system itself. Both amines overcome the deleterious effects of anesthetics upon the heart. The heart tends to fail when the hormones are absent. The epinephrine and norepinephrine content of the adrenal gland has been compared without and during anesthesia. A depletion is consistently noted. This has been offered as presumptive evidence of a sympatho-adrenal response. Anoxia, CO_2 excess, ether, chloroform and spinal anesthesia all cause a depletion of the epinephrine content of the gland. Unexplained, unexpected deaths were, years ago, ascribed to ventricular fibrillation due to the sudden rapid, excessive release of epinephrine from the adrenal gland in the presence of increased cardiac irritability from anoxia, cyclopropane, chloroform and other cardiac sensitizing drugs. Valid biochemical data in support of this hypothesis have never been presented. Indirect evidence of sympathetic stimulation, such as tachycardia, elevation in blood pressure, hyperglycemia and disturbances in carbohydrate metabolism have been offered to support the contention that ether, chloroform anesthesia and anoxia are accompanied by sympathetic stimulation. Epinephrine blood levels have been determined but the data presented have been open to question, either because the analytical method did not differentiate between epinephrine and chemically related catechol amines, the epinephrine precursors

or because they were not sufficiently sensitive to accurately portray the blood level. Price and his associates have come the closest to providing definitive blood level data on both epinephrine and norepinephrine. They found, utilizing the trihydroxyindole method for analysis, that the plasma norepinephrine level was elevated during cyclopropane anesthesia in man. The variations paralleled the depth of anesthesia. Erratic responses in plasma norepinephrine occurred during ether anesthesia. Little or no change was noted with thiopental or halothane (Fluothane) anesthesia. Elevations in epinephrine levels were erratic and not consistent. Their data indicates that the adrenal gland plays a minor role in the sympathetic response and in elevating catechol amines. The response is largely due to norepinephrine release from adrenergic structures other than the adrenal glands.

EPINEPHRINE

Properties

Epinephrine is a white powder, sometimes tinted slightly brown. Its molecular weight is 183. The base melts at 211° to 212°C. The free base is slightly soluble in water and alcohol. It is insoluble in chloroform, ether and acetone. Solutions of the free base are neutral to litmus, but alkaline to more sensitive indicators. The base combines with acids to form water soluble salts. The hydrochloride is the most common salt. The optical rotation of the hydrochloride in aqueous solutions is

$$[\alpha]_D^{25°} \ -50° \text{ to } -53.5°.$$

Solutions are unstable. The drug is readily oxidized to adrenochrome and other brown oxidation products. It is stored in amber bottles to protect them from light which hastens their deterioration. The U.S.P. strength of epinephrine hydrochloride solution is 1/10th of a gram of the drug per 100 ml. of physiological saline. Dilute solutions are less stable than concentrated. Concentrated stock solutions are therefore dispensed which are diluted to proper strength at the time of use. A suspension of epinephrine in peanut oil (0.2%) often referred to as "slow epinephrine" is made available for intramuscular injection. The slow absorption of the drug from the oil results in a prolonged sustained effect. Tablets of the borate and bitartrate are available for preparing solutions for local anesthesia. A glycerol solution (1 part in 1000) is available for inhalation by nebulization. Ointments (1 in 100) in a petrolatum base are available for topical use.

The U.S.P. requires standardization of epinephrine by biological assay on dogs anesthetized with ether and treated with atropine and curare. The standard dose is one which elevates the blood pressure 30 mm. to 60 mm. Hg from a base level in a standard weight dog. Other biological methods of assay are based upon the relaxing effect of the drug on mammalian uterine muscle or upon the sphincter muscle of the pupil of the sympathectomized eye. Only the levorotatory drug is employed clinically. The racemic form is available but possesses half the physiological action of the levo form. Epinephrine is also known by various proprietary names, most common of which are Adrenaline and Suprarenin.

NOREPINEPHRINE

Norepinephrine, or more accurately levoarterenol, is a base which forms a

colorless, odorless, crystalline monohydrate salt with tartaric acid. As is the case with epinephrine, contact with air, oxidizing agents and alkalies causes it to decompose. Norepinephrine is more stable to oxidation than epinephrine. A neutral aqueous solution is stable for many hours at room temperature. Heating to 100°C. for one hour completely inactivates the compound. In alkaline solution it is completely inactivated at room temperatures. Levo-norepinephrine bitartrate melts at 163°C and has an optical rotation of $[\alpha]_D^{25°} -37°$. The hydrochloride melts at 146°C. and has an optical rotation of $[\alpha]_D^{25°} -40°$. The U.S.P. solution is made isotonic with saline and stabilized with 0.2% sodium bisulphite which prevents oxidation of phenolic compounds to quinones. The solution is available in 4 ml. ampules of 0.2% strength which is equivalent to 0.1% base. The inactivation in the body presumably follows the same pathway as does epinephrine.

The d,l mixture has been known for years. In 1948 Tuller resolved the mixture by taking advantage of the difference in solubility of the two isomers in methanol. The levoarterenol bitartrate forms a hydrate which is soluble in methanol. The dextro derivative does not form a hydrate and has a low solubility in methanol. Heating of the acid solution causes racemerization of the optical isomers. Similar behavior is noted with epinephrine.

EPHEDRINE

Chemistry

Ephedrine is the prototype of a series of several hundred synthetic adrenergic drugs used in current therapy. It has, to a certain extent, been superseded by other drugs but still remains as one of the more important pressor agents. Ephedrine is a constituent of the herb Ma Huang and has been used for treatment of respiratory diseases for over five thousand years in China. The drug is an alkaloid occurring in groups of plants belonging to the genus *ephedra* which is indigenous to India, Spain and other geographic areas of about the same latitude. The plants, which grow as stalks without branching, are related to pines, ferns, and other gymnosperms. The alkaloid, first isolated in pure form by Nagi (1887) was studied in a general way by Takahashi and Miura (1892). The drug was considered toxic and was, therefore, little used before 1917 except for mydriasis. Later it was reinvestigated by Amatsu and Kubota. Chen and Schmidt (1923) reported extensive pharmacological studies and actually rediscovered the compound.

The molecule has two asymmetric carbon atoms. In the plant two forms of the drug exist, *levo ephedrine* and *dextro pseudo ephedrine*. The levo ephedrine, which is the official substance, is found in the Chinese plant while the other plants contain mixtures. Four optically active isomers are possible due to these two asymmetric carbon atoms. Therefore, a total of six stereo-isomers is possible: l, d, and dl, ephedrine, and l, d, and dl, pseudo ephedrine. The levo ephedrine is more active physiologically than the levo isomer. Dextro pseudo ephedrine is next in activity. The pseudo ephedrines differ somewhat from ephedrine in clinical, physical and pharmacological properties. The OH and CH_3 groups in ephedrine are close to each other, while in pseudo ephedrine they are farther apart.

Source

Until recent years most of the drug was derived from plant sources. The shortage which developed during World War II stimulated interest of the synthetic products. Both the racemic form, known as ephtonin and the levo form are available for medical use. Ephitonin is less active than the levo form. The pure levo form is made by fermentation of glucose with yeast in the presence of benzaldehyde.

Ephedrine manifests many of the physiological reactions of epinephrine but over a longer period of time. The drug has greater stability to air, light, heat and pH changes then epinephrine. The greater stability is due to the absence of hydroxyl groups on the benzine nucleus, and to the presence of the methyl group on the alpha carbon. The drug is effective orally. Adrenergic agents possessing the unsubstituted phenyl ring and a methyl group on the carbon atom are cortico-medullary stimulants. Ephedrine is resistant to amine oxidase. This refractoriness to this enzyme is due to the presence of the alpha methyl group. The exact fate of ephedrine in the body is not known. The destruction in heart-lung preparations and other perfusion systems is slow. Some deamination occurs aided by the ascorbic-dehydro ascorbic acid enzyme system. Thorp, Essex, and Mann found undiminished pressor activity even after three hours of perfusion through animal tissues. As much as 40% of a therapeutic (50 mgm.) dose of ephedrine is excreted unchanged into the urine.

Since the alkaloid is a base, it forms salts with mineral and other acids. The *hydrochloride* and *sulphate* are U.S.P. official preparations. Both salts are soluble in water; the free base is only

slightly so. The alkaloid is soluble in oils and petrolatum bases, however, and is used in the form of a 1% ointment in petrolatum for topical application. The anhydrous alkaloid is a colorless, unctuous solid which liquefies easily and boils at 132° to 133°C. The melting point is not sharp due to variations caused by the absorption of moisture. The free base is soluble in alcohol, chloroform, and ether. Solutions of the base are strongly alkaline to litmus. The optical rotation of the free base at 25°C. is —33° to —35.5° using a sodium light. A hemihydrate forms with water, which is stable. Ferric chloride, unlike epinephrine, does not cause a purple coloration when added to ephedrine, since there is no hydroxyl group on the aromatic ring. Ephedrine and its salts give a red-purple color when added to a reagent containing 1% solution of hydrochloric acid and 10% copper sulphate after which is added a 20% caustic soda solution. Solutions of ephedrine do not turn brown on standing due to the absence of the phenolic hydroxyl groups. The hydrochloride of the levo form melts between 216° to 220°C.

AMPHETAMINE

A number of drugs chemically and pharmacologically allied to ephedrine are used for their sympathomimetic effects. Omission of the methyl group on the amino-nitrogen without other changes results in propadrine; replacement of both the methyl group on the amino nitrogen and the hydroxyl group on the beta or (phenyl bearing carbon) with hydrogen results in amphetamine; replacement of only the hydroxyl group on the beta carbon of ephedrine results in methamphetamine (Methedrine, desoxyephedrine, Desoxyn). A second methyl

group instead of a hydrogen atom on the alpha (amino bearing carbon) results in mephenteramine (Wyamine).

PHENYLEPHRINE (NEOSYNEPHRINE) AND RELATED HYDROXY PHENYL DERIVATIVES

Phenylephrine (Neosynephrine) is widely employed as a pressor substance for hypotension due to spinal anesthesia and other syndromes characterized by vasodilatation. It differs from epinephrine in having only one hydroxyl group. This is in the meta (3) position with reference to the aliphatic chain. Since it is chemically allied to epinephrine in many ways it responds pharmacologically and reacts chemically as does epinephrine. Solutions readily oxidize in air to brown products, such as quinones and melanins. A purple color forms when ferric chloride is added to aqueous solutions. The free base forms salts with mineral acids, the most important of which is the hydrochloride. The salt consists of white crystals which are odorless and bitter to taste. The melting point varies between 140–145°C. Phenylephrine is less potent than epinephrine or norepinephrine and has a longer duration of action. Its rate of inactivation is slower than that of ephedrine. It lacks central effects and does not sensitize the heart to hydrocarbon anesthetics. Neosynephrine has an asymmetric carbon atom and possesses optical activity. The rotation is:

$$[\alpha]_D^{25°} - 46.2°$$

Solutions are acid to litmus.

OTHER HYDROXYPHENYL AMINES

A number of other variants of epinephrine are formed by shifting the hydroxyl groups on the phenyl nucleus or the groups on the aliphatic chain or on the amino groups to other positions. Shifting the methyl group from the amino nitrogen atom of phenylephrine to the alpha carbon results in Aramine. The para (4) hydroxy derivative is known as *Synephrin* or Synthenate. This is isomeric with phenylephrine. Shifting the methyl group from the nitrogen atom to the alpha carbon results in *hydroxy amphetamine* (Paradrine). Shifting the methyl group of epinephrine from the amino to the alpha carbon results in *Cobefrin* (Corbasil). Converting this methyl group to an ethyl results in *butanephrine*. Converting the methyl group on the amino nitrogen to an isopropyl group results in *isopropylarterenol.*

All the hydrophenyl derivatives respond to most of the tests characteristic of phenols.

METHOXAMINE (VASOXYL) AND OTHER METHOXAMINE DERIVATIVES

The methoxy group may appear on the phenyl group instead of the hydroxyl. The 2, 5 dimethoxyphenyl substitution on propadrine results in methoxyphenylamine (methoxamine U.S.P., Vasoxyl). Methoxamine forms a hydrochloride which melts between 212–216°C. One gram dissolves in 2.5 ml. of water.

ANTI-ADRENERGIC DRUGS
Chemical Types

Drugs which block adrenergic activity exert their effect by intervening between the effector cells and the hormones of the adrenal medulla or the adrenergic mediators (epinephrine and norepinephrine). Sometimes these substances are referred to as *adrenolytic* and *sympatholytic* substances. These terms are less desirable than the term *adrenergic blocking agent.* Substances possess-

ing such activity are both naturally-occurring and synthetic. The naturally-occurring substances are derived from *ergot*. Semi-synthetic derivatives may also be prepared from these alkaloids which manifest varying degrees of blocking activity or which have their side effects attenuated.

The first of the synthetic compounds of this type which were made available were the *dioxanes* of which piperoxan (933F, Benodaine) is the better known. Another series is prepared from the *beta-haloalkylamines*. Of this group dibenzyl chloroethylamine (Dibenamine) and phenoxyisopropyl amine (Dibenzylene) are the most important. Another series consists of derivatives of *imidazoline* of which phentolamine (Regitine) and tolazoline (Priscoline) are the most important. Another group is composed of derivatives of *dibenzozaphine* of which azeptine and dibenzozane are the most important. Other compounds are extracts of Galium, Asparine and Rauwolfia, the phenozyethylamines, isoquinolines, etc. A detailed discussion of these substances is not possible here.

Relationship of Structure to Activity

The tertiary amino group appears most consistently on the molecule of all the useful synthetic anti-adrenergic compounds. Quaternization of the nitrogen atom abolishes adrenergic blocking activity. Presumably the haloalkylamine group is not essential for activity since the imidazoline, the diaxanes, and the dibenzozaphine derivatives do not possess this grouping and are active to the same degree as the haloalkanes.

None of the blocking drugs interferes with the release of epinephrine or norepinephrine. They neither alter nor destroy these agents. They have no influ-ence on the responses of drugs which directly stimulate smooth muscle. The blocking agent presumably becomes fixed at the receptor site which ordinarily binds the adrenergic neurohormone. The synthetic blocking agents act principally at the alpha receptors. Large doses block the beta receptors (30–100 times larger). The ergot alkaloids are ineffective at the alpha receptors but appear to exert their effects at the beta. Ergonovine appears to act at the beta receptors.

Excretion

The ergot alkaloids are destroyed in the body presumably in the liver. Little or none appears in the urine. Dibenamine is lipophilic and remains in the body 18 hours or more. Its fate in the body is not known, but its diffusion from body stores is slow.

AMINE OXIDASE INHIBITORS

The exact counterparts to the anticholinesterases found in the parasympathetic division are not known in the sympathetic system. Amine oxidase inhibitors are available but these act in the brain and augment the action of amines liberated there. Their peripheral effects are of no clinical importance in producing sustained sympathetic stimulation. However, these compounds are described further on in this chapter.

DRUGS ACTING AT THE AUTONOMIC GANGLIA

NEUROHORMONAL ACTION AT THE GANGLIA

The transmission of impulses from preganglionic fibres to postganglionic fibres at the ganglia in both the sympathetic and parasympathetic divisions of

the autonomic nervous system is mediated by acetylcholine. The acetylcholine depolarizes the cell bodies of the postganglionic neurons and thereby initiates the impulse in the postganglionic fibre.

CHEMICAL TYPES OF GANGLIOLYTIC DRUGS

Considerable attention has been directed to the study of substances which affect the ganglia, particularly drugs which produce a block at this site. Many quaternary bases and some tertiary amines manifest ganglionic blocking effects. Some have several actions since they act at several sites. Tubocurarine, for example, is a neuromuscular blocking agent for striated muscle. In large doses, however, it also blocks at the ganglia. Methantheline (Banthine) blocks at the postganglionic cholinergic receptors of the autonomic nervous system primarily, but it also acts to a lesser extent at the autonomic ganglia.

The drugs of chief interest which act on the ganglia are those which cause a blockade. Nicotine and acetylcholine both cause a blockade. The action of these, however, is biphasic; that is, they exert two effects. Both drugs first stimulate, then they paralyze the ganglia. Presumably they depolarize first and keep the ganglia depolarized so that the acetylcholine released from subsequent impulses fails to act. Thus, acetylcholine, in large doses, may also cause a block. Drugs which stimulate the ganglia are of little clinical interest and have, therefore, not been studied in detail and will not be mentioned here.

Ganglionic blocking drugs have received wide clinical application for a variety of purposes but chiefly as antihypertensive drugs. Their chief use in anesthesia has been for decreasing the peripheral resistance to reduce an abnormally elevated blood pressure or to deliberately reduce the blood pressure to subnormal levels to avoid blood loss. Numerous drugs have been introduced for their vasodilating qualities. A detailed discussion of these is beyond the scope of this book. Only those directly applicable to anesthesiology will be considered.

MODE OF ACTION OF GANGLIOLYTIC DRUGS

Most ganglionic blocking agents act at the receptors in the ganglia where acetylcholine acts. In contrast to acetylcholine they block the transmission across the synapse without causing depolarization of the neuronal cell body. They do not prevent the release of acetylcholine from the terminal membranes of the preganglionic nerves, but they inhibit the stimulating action of acetylcholine at this site. The action is most likely competitive, because higher doses of stimulating agents overcome the block. It is not surprising, therefore, to find a close resemblance between blocking agents and acetylcholine.

Relationship of Structure to Activity

The majority of ganglionic blocking agents are quaternary bases. As early as 1914 it was recognized the *tetraethyl ammonium salts* produced ganglionic block and that its effects were limited to this action, by and large. This compound is ammonium hydroxide with its hydrogen atoms substituted by ethyl groups (C_2H_5)$_4$ NCl. Methyl substitution appears to produce compounds with neuromuscular blocking activity. The ganglionic blocking qualities of the methonium compounds has been discussed under muscle relaxants (Chap.

23). Those in this series which have had widespread clinical use are hexamethonium and pentamethonium. Shortening the carbon chain negates the muscle relaxant properties (exemplified by C_{10}, decamethonium) and accentuates ganglionic blocking effects. Ganglionic blocking effects appear when acetylcholine is modified. Ethyl substitution on the amino nitrogen favors a gangliolytic action. Carbachol is more effective in this regard than methacholine. It is not necessary that the compound have a quaternary nitrogen atom to manifest a ganglionic block effect, however. Procaine, atropine and epinephrine all possess some degree of gangliolytic activity when given in large doses. None is a quaternary base, since procaine and atropine are tertiary amines and epinephrine a secondary.

Mention has been made that other pentavalent elements may replace nitrogen in the molecule of the "onium" compounds and the substance still produces myoneural blockade (Chap. 23). Presumably this also applies to the gangliolytic effects of these drugs. One hypotensive drug in widely used anesthesiology, Trimethaphan (Arfonad) contains a sulphur atom in the cationic portion of the molecule. This is discussed below. The anticholinesterases act at the ganglia in a manner similar to that which they exert at the endplate and thus inhibit ganglionic transmission. These substances all ionize in aqueous solutions to form an active cation and an anion. The cationic head is physiologically active and is the one which becomes attached to the receptor.

Quaternary ammonium compounds are poorly absorbed from the gastrointestinal tract. Doses administered parenterally are filtered by the kidney and pass almost in toto into the urine. The distribution in blood and tissues is believed to be similar to that of the muscle relaxants. Most of a given dose is distributed to the extracellular fluid compartments of the body before the kidney undertakes its elimination.

TRIMETHAPHAN (ARFONAD)

The most extensively used of the gangliolytic drugs from an anesthesia standpoint is Trimethaphan. This substance is an ultra short acting derivative with an evanescent, transient action which gives it a degree of controlability not possessed by other agents. The structure is complex. It is built around a thiophanium nucleus to which are attached at the 2 and 4 positions a 2 keto imidazolido nucleus upon which are substituted two benzyl groups, one in the 1 position and one in the 3 position. A cyclic trimethylene group is attached to the sulphur atom of thiophanium.

The drug is quickly metabolized in the body. Only 20-40% of an injected dose are recovered in the urine and all of this within three hours after injection.

HEXAMETHONIUM

Hexamethonium is a white crystalline powder whose structure is similar to decamethonium, only the chain has six carbon atoms. It is soluble in water and alcohol. The base is available as the chloride which forms acid solutions (pH 5.5-6.5) in water. It becomes distributed in the extracellular fluid. As is the case with other quaternary bases absorption is poor from the gastrointestinal tract. It is cleared from the blood by the glomeruli. Over 90% of a dose may be recovered in the urine within 24 hours although 60% appears within 3 hours.

CHEMICAL MEDIATORS, NEURO-HORMONES AND CEREBRAL METABOLISM

Norepinephrine, acetylcholine and serotonin are organ specific substrates involved in nerve function. Acetylcholine and norepinephrine have been dealt with in the preceding discussion. Serotonin, however, has not been described. It has been postulated that two opposing systems are present in the subcortical area of the brain, particularly the diencephalon which regulates autonomic and extra-pyramidal motor functions. These are referred to as the *trophotropic* and the *ergotropic* systems. The ergotropic system integrates functions which physiologically involve body work. It increases sympathetic responses, increases activity of skeletal muscle and causes arousal of psychic states. The trophotropic system opposes the ergotropic and produces parasympathetic effects, a decrease in muscle activity and a decrease in response to external stimuli. The possibility that serotonin is the neurohormone of the trophotropic system and norepinephrine of the ergotropic system has been postulated. Both substances are formed in the brain and stored there in bound form. They appear to be concentrated in those areas which seem to control these neurofunctions.

METABOLISM OF SEROTONIN

The precursor of serotonin is 5-hydroxytryptophane. Presumably, tryptophane is first hydroxylated and then decarboxylated by tryptophane oxidase, a decarboxylase. Serotonin was isolated in pure form in 1948. Prior to that time the substance was detected by biological assay of its pressor effect and was referred to as *enteramine*. The reason for this nomenclature is that the substance was first isolated from the certain chromaffin cells found in the gastro-intestinal mucosa. The substance is sometimes referred to by abbreviation of its chemical name as 5HT. Serotonin is an indole derivative. Its formation from tryptophane is represented as follows:
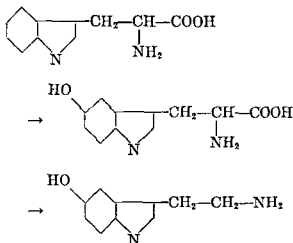
Serotonin is stored in the tissues in an inactive, bound form. Free serotonin may be released in vivo. Serotonin is found, as has been indicated, in the brain, the gastro-intestinal tract and in blood. The serotonin in blood is found in the platelets from which it is released when they disintegrate. The highest concentration in the brain is found in the hypothalamus. Other areas which have an abundance are the area postrema, mesencephalon, nuclei of gracilis and cuneatus, floor of the fourth ventricle and grey matter of the cord. The cerebral cortex and white matter contain little or no serotonin. The normal serum level is approximately 0.1 microgram per ml.

Serotonin is inactivated by monamine oxidase to 5 hydroxyindol acetic acid:
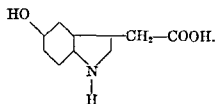
This oxidase occurs in the brain. Evidence of decarboxylic activity by which serotonin is formed from its precursors is also found in the brain although the kidney, gastro-intestinal tract and liver have high activity also.

EFFECTS ON BRAIN FUNCTION

The hypothesis that autonomic, somatic and psychic functions in the brain are maintained in a balanced state by opposing systems has some appeal. It helps explain the effect of psychotherapeutic agents and changes in behavior induced by these agents. Reserpine, for example, stimulates the trophotropic system. Chlorpromazine blocks the ergotropic system. Reserpine interferes with the metabolism of serotonin and impedes the ability of the brain to store serotonin. The cells can no longer bind the amine. The synthesis is not impaired, however.

Chlorpromazine acts as an antiadrenergic substance in the brain and blocks the action of norepinephrine.

Brodie postulates that a drug may block the trophotropic system, and, in this manner, accentuate ergotropic effects or it may stimulate the ergotropic system. Certain indoles, as, for example, lysergic acid diethyl amide, are believed to interfere with the action of serotonin at the synapses. Many ergotropic agents, on the other hand, are congeners of norepinephrine which penetrate the brain easily. They act at ergotropic synapses. Compounds, such as mescaline, amphetamine and desoxyephedrine act in this manner. Much of this is conjecture and additional data is necessary to conclusively clinch this postulate as actual fact. Such data are not available at the moment. These findings also suggest that mental disease has a chemical basis.

Neuromuscular Blocking Agents

SITES OF ACTION OF MUSCLE RELAXANTS

THE USE of skeletal muscle relaxants as adjuncts to anesthesia is commonplace. Muscle relaxation is caused by inactivation of a muscle fibre. A muscle is composed of a multitude of individual fibres. The degree of relaxation of a muscle depends upon how many individual muscle fibres are inactivated. A variety of drugs may cause this inactivation. Skeletal muscle relaxants act at one or more of the following sites: (1) Centrally at the motor neurons or their synapses in the cerebrum or the basal ganglia, (2) at the synapsis of motor pathways to the anterior horn cells in the spinal cord, (3) on the motor nerve fibres themselves as they leave the cord (4) at the myoneural junction (neuromuscular synapse) and (5) on the muscle fibre itself. General anesthetics, sedatives, and anticonvulsants produce their effects by acting centrally in the brain. Mephenesin, zoxazolamine and meprobamate are representative of drugs which decrease the frequency of impulses passing over the internuncial neurons to the motor cells in the spinal cord. Local anesthetics block the transmission of impulses along the nerve fibres. Neuromuscular blocking agents, such as curare and its allies, exert their effects at the neuromuscular junction. Quinine is an example of a drug which exerts part of its relaxing effect by acting directly on the muscle fibre. It suppresses activity by prolonging the refractory period.

The drugs which have been found to be most useful as adjuncts to anesthesia exert their effects at the neuromuscular junction. Therefore, this discussion will be limited to compounds which act at this site.

BIOCHEMICAL ASPECTS OF NEURO-MUSCULAR ACTIVITY

In order to understand the relationship of chemical structure of relaxants to pharmacologic behavior it is necessary to briefly review the biochemical aspects of neuromuscular transmission.

THE MYONEURAL JUNCTION

The nerve impulse is an electrical current (action potential) which originates in the anterior horn cell and passes along the axone to the muscle fibre. A neuron is a biological unit designed for transmission of stimuli from one cell to another. The terminal portion of the axone merges into the sarcoplasm of the muscle fibre. The portion of the neural membrane at the termination of the axone which faces the muscle fibre is called the *terminal membrane* (Fig. 1.23). Overlying the muscle fibre beneath the terminal membrane is a specialized membrane known as the *post-junctional membrane*. The terminal membrane, thus, faces the post-junctional membrane. This area of union of nerve and muscle is referred to

471
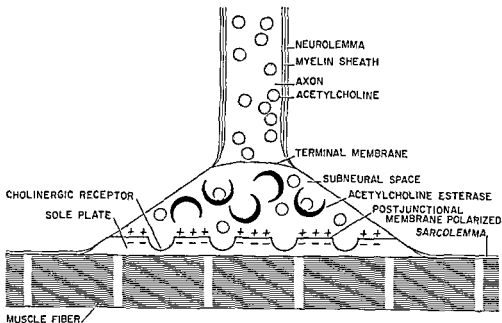
FIG. 1.23. Schematic representation of the resting endplate. Note that the postjunctional membrane is polarized. (Courtesy of Francis Foldes.)

as the *end plate*. The terminal membrane and the post-junctional membrane, are separated by a space referred to as the *subneural space*. The post-junctional *membrane is permeable to various ions* most important of which, as far as this discussion is concerned, are those of sodium and potassium. This permeability is not necessarily limited to these two ions, however. As a result of the semi-permeability, differences in concentration of ions develop which create an electrical imbalance and a difference in polarity between the exterior and the interior of the post-junctional membrane. The interior aspect of the post-junctional membrane faces the muscle fibre; the exterior faces the end of the axone. During the resting phase of a muscle-nerve preparation the exterior of the post-junctional membrane is positively charged while the interior is negatively charged. A membrane in this state is said to be *polarized*. This difference in polarity is due to the preponderance of potassium ions at the interior surface

and sodium ions on the exterior of the membrane. The *electrostatic difference in potential* in mammalian muscle between the exterior and the interior of the membrane is approximately 90 millivolts.

Depolarization

The nerve impulse causes the liberation of *acetylcholine* when it arrives at the terminal membrane. Acetylcholine, presumably, normally is bound or adsorbed to the proteins in one of the membranes. Whether or not it originates from the protein of the axone or that of the post-junctional membrane is not definitely established. Immediately upon release it is adsorbed to the proteins in the cholinergic receptors of the post-junctional membrane. Whether or not the electrical impulse jumps the subneural space and causes the liberation of acetylcholine at the post-junctional membrane or whether the acetylcholine is released at the terminal membrane of the nerve fibre and passes through the subneural space to the post-junctional membrane

is a debatable point. The acetylcholine alters the molecular configuration of the proteins in the post-junctional membrane. This in turn results in a change in permeability. This altered permeability makes possible the migration of potassium ions outward and sodium ions inward. This interchange of ions initially causes a decrease and then a disappearance in the negativity of the electrical charge in the interior of the post-junctional membrane. The decrease of negativity towards zero is referred to as *depolarization*. The negativity of the electrostatic potential may not only be re-duced to zero, but, the ionic migration may be such that the charge on the interior of the post-junctional membrane may even become positive. As long as the potential does not decrease below minus 45 millivolts all the electrical activity remains localized at the end plate. The range of negativity between minus 90 to minus 45 millivolts in referred to as the *end plate potential* (Fig. 2.23). As the potential falls below this critical level of minus 45 millivolts the electrical activity spreads to the parts of the muscle fibre adjacent to the end plate and sets up electrical activity known as the
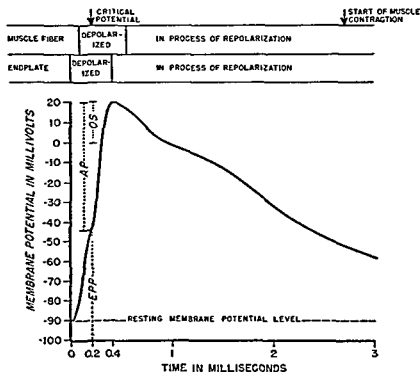
Fig. 2.23. E P P endplate potential; A P action potential; O S overshoot. Due to the release of acetylcholine by the *nerve impulse* at the endplate at zero time the endplate potential is generated and in about 0.2 milliseconds the resting membrane potential of the endplate (−90 millivolt) decreases to −45 millivolts. When this critical level is reached the potential change, from here on termed action potential, becomes propagated, within another 0.2 milliseconds overshoots and becomes electro-positive (+15–20 millivolts). Within the next 2 to 3 milliseconds the endplate becomes repolarized and when the polarization process is almost complete the contraction of the muscle fiber starts. (Courtesy F. Foldes, *Muscle Relaxants in Anesthesiology*. Springfield, Thomas, 1957.)

action potential. This action potential causes the muscle fibre to contract. The membrane potential usually *overshoots* zero and becomes positive to a magnitude of plus 30 millivolts. The exterior of the membrane, of course, becomes negative when this happens.

Repolarization

Depolarization occurs very rapidly. The time necessary for depolarization ranges between 0.2 to 0.4 milliseconds. The end plate becomes depolarized between 0.2 to 0.3 milliseconds. During this interval of time the acetylcholine is hydrolyzed to acetic acid and choline by an enzyme known as *acetylcholine esterase* (true cholinesterase). This enzyme is present in the junctional membrane. As this hydrolysis occurs the permeability of the junctional membrane is restored to that of the normal resting state. The potassium ions return inward and the sodium outward as the permeability is restored. The membrane potential first drops to zero from 30 millivolts positive and then shifts to negative and becomes increasingly negative until it is restored to the 90 millivolts difference. The exterior once again becomes positive. The membrane is then said to be *repolarized.* It is then once again ready to receive the next burst of acetylcholine liberated by the ensuing nerve impulse.

The muscle fibre does not contract immediately upon depolarization of the membrane. Instead, there is a lag of 2 to 3 milliseconds before contraction of the fibre commences. Thus, the repolarization of the end plate is completed by the time the fibre begins to contract.

THE ROLE OF ACETYLCHOLINE IN NEUROMUSCULAR TRANSMISSION

The acetic acid and choline recombine to form acetylcholine. This resynthesis is aided by a second enzyme known as *choline acetylase.* Presumably different proteins are present in the end plate to which acetylcholine is adsorbed or bound at one time or another during the processes of depolarization and repolarization. In the resting phase acetylcholine is stored by being bound to one of these proteins from which it is released by the neural impulse. After release it is next bound to a second one in the end plate, known as the *cholinergic receptor,* after which depolarization occurs. A third protein is associated with the forementioned choline acetylase which facilitates the resynthesis of acetylcholine from the acid and choline. Interference with the enzymatic hydrolysis of acetylcholine causes sustained depolarization. The rapid removal of acetylcholine is mandatory for repolarization and continued activity in a muscle fibre.

It is obvious from the foregoing discussion that flaccidity of skeletal muscle develops if an agent (1) interferes with the transmission of a nerve impulse or (2) interferes with the liberation of acetylcholine, or (3) interferes with depolarization and repolarization of the end plate, or (4) depolarizes the membrane and keeps it depolarized. Procaine applied to an axone prevents transmission of the impulse along the axone. Botulinus toxin, procaine, and the hemicholiniums cause a reduction of the output of acetylcholine at the terminal membrane and, thus, inhibit activity. These act pre-synaptically. Curare and its pharmacologic congeners interfere with depolarization or repolarization or both. Decamethonium causes persistent depolarization. They act post-synaptically. The last two types of agents are grouped together and called *neuromuscular blocking agents.* This group is the one of interest in anesthesiology.

TABLE I.23

$$H$$
$$H-N-H$$
$$H \quad Cl$$

Ammonium Chloride

$$C_2H_5$$
$$C_2H_5-N-C_2H_5$$
$$Cl \quad C_2H_5$$

Tetra Ethyl Ammonium Chloride

$$\begin{matrix} O & H & H & Cl & CH_3 \\ CH_3-C-O-C-C-N-CH_3 \\ & H & H & CH_3 \end{matrix}$$

Acetyl Choline Chloride

$$\begin{matrix} CH_3 & & A^\circ & CH_3 \\ CH_3-N-(CH_2)_n-N-CH_3 \\ CH_3 & & & CH_3 \end{matrix}$$
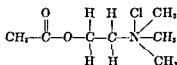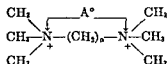
Bismethonium Compounds

n = 6 = Hexamethonium
n = 5 = Pentamethonium
n = 10 = Decamethonium
(A° = 14)

MECHANISM OF NEURO-MUSCULAR BLOCKADE

Acetylcholine is a quaternary base (Chap. 22). A quaternary base is ammonium hydroxide with one or more of its hydrogen atoms replaced by an organic radical (Table I.23). Numerous choline-like quaternary bases exist. On close inspection it is noted that they act in a manner similar to acetylcholine but with varying degree of intensity. Examination of other quaternary bases not related to choline reveals that they too exert some action at the myoneural junction. Examination of the chemical structure of muscle relaxants reveals that the majority are quaternary bases. The bases which show activity differ from acetylcholine and do so in two respects: (1) they are not hydrolyzed or if they are the breakdown occurs slowly compared to that of acetylcholine or (2) they are bound preferentially, and with greater tenacity than acetylcholine, to the proteins of the cholinergic receptors.

From the standpoint of pharmacologic behavior two groups of neuromuscular blocking agents are recognized. In the first group are substances which are adsorbed to the cholinergic receptors and prevent acetylcholine from exerting its depolarizing effect. These are called *non-depolarizing* agents. They themselves are incapable of depolarizing the junctional membrane. Their action is a restraining one. Acetylcholine continues to form but the drug prevents it from acting at the end plate. Such substances act by the mechanism referred to as *competitive inhibition* (Chap. 24). Some evidence exists that they may reduce the degree of depolarization. For this reason the term *anti-depolarizers* has been proposed as being more descriptive. They apparently form a more stable and persistent union with the protein in the receptors. In the second group are substances which cause persistent depolarization of the post-junctional membrane. These are referred to as *depolarizing* agents. Some quaternary bases exert a dual effect. They depolarize under certain circumstances and they block acetylcholine under others. Substances which cause neuromuscular blockade by either or a combination of these two mechanisms are sometimes referred to as *curaremimetic substances*.

CURAREMIMETIC SUBSTANCES

Curare is the oldest known muscle relaxant. The active principles of curare are alkaloids which are complex quaternary bases. Numerous synthetic muscle relaxants have recently been introduced. All of these, likewise, are quaternary bases.

QUATERNARY BASES

The most important and the most extensively studied of the curare alkaloids is *tubocurarine*. The molecule of tubocurarine carries two quaternary nitrogen atoms. The presence of quaternary nitrogen atoms on tubocurarine focused attention on the quaternary bases as a group and lead to the finding that many cations derived from quaternary bases are capable of causing curare-like blockade of neuromuscular transmission. Barlow and Ing were prompted to test a series of substituted ammonium compounds for neuromuscular blocking activity. They found that the alkyl substituted derivatives, particularly, showed some degree of curaremimetic activity. In many instances, though, the action is too feeble to be clinically effective. In addition to the neuromuscular blocking effect, many quaternary bases inhibit synaptic transmission in the autonomic ganglia. Tetraethylammonium chloride (Table I-23), one of the simpler of the quaternary ammonium compounds, and most of its homologues, are ganglionic blocking agents. They behave like nicotine in this respect. Quaternary bases, therefore, have a dual effect. They cause both neuromuscular and autonomic blockade. Methylation of a quaternary base imparts a depolarizing activity to the compound, particularly to one of the non-depolarizing type. Interchanging methyl groups for ethyl groups on such a compound reduces curaremimetic activity but retains or enhances ganglionic blocking effects.

"ONIUM" COMPOUNDS

Further study showed that the nitrogen atom is not essential for neuromuscular blocking activity of a quaternary base. Other elements having a valence of 5, such as arsenic, phosphorus and so on which can form alkyl substituted quaternary bases in the same manner as nitrogen are likewise effective. Series of compounds formed from pentavalent elements including nitrogen are referred to as *onium* compounds. Phosphorus forms *phosphonium* derivatives, arsenic *arsonium*, antimony *stibonium*, sulphur *sulphonium* and iodine *iodonium* salts. Although "onium" compounds derived from these elements are pharmacologically similar to those derived from nitrogen none has any clinical applicability because they possess other (side) effects which are objectionable. Apparently this muscular blocking effect is characteristic of onium derivatives as a class.

SALTS OF QUATERNARY BASES

The onium compounds are bases and, therefore, form salts with acids in the same manner that ammonium hydroxide forms salts with an acid. The salts ionize to a basic cation, which is the counterpart to the ammonium ion, and an anion, which is derived from the acid portion of the molecule. This ionization is similar to that of ammonium salts and is represented as follows:

$$NH_4Cl \rightarrow NH_4^+ + Cl$$

$$NR_4Cl \rightarrow NR_4^+ + Cl$$
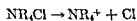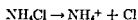
The onium ions are positively charged. Ing and Wright (1932) noted that curaremimetic activity is a function of the onium ion and is independent of the groups attached to the central atom and of the central atom itself as long as this atom has a central localized positive charge. This element making up the central atom may be any of the forementioned pentavalent atoms. The nitrogen atoms in tubocurarine are attached to cyclic structures which establishes a dis-

tance of 12.5 A° between them. It became apparent in studying compounds with curaremimetic activity that derivatives having two quaternary nitrogen atoms at a distance of approximately 15 A° showed the greatest degree of curaremimetic activity. This prompted the preparation of compounds of simpler molecular configuration. It also led to attempts to imitating the structure of tubocurarine.

INTERNITROGEN DISTANCES AND ACTIVITY

Barlow and Ing centered their interest in the blocking activity of a number of onium compounds in which the nitrogen atoms were directly attached to the terminal carbons of polymethylene chains of different lengths. The term polymethylene refers to a straight chain composed of a series of carbon atoms (CH_2 groups). The neuromuscular blocking potency was greatest when each quaternary nitrogen atom was separated from the other by a chain of ten carbon atoms and when each nitrogen atom had three methyl groups (Table I.23). Synthesis of the polymethylene series verified the fact that the selectivity of action of quaternary bases at the neuromuscular junction depended upon the separation of the nitrogen atoms at some optimal distance and that this distance, roughly speaking, is 14 or 15 A° or a distance of ten carbon atoms in a chain. An inter-quaternary distance of 15 A° is not a mandatory requirement for adequate neuromuscular blockade, however. Compounds exist manifesting curaremimetic activity whose inter-nitrogen distances are more or less than 15 A°. The distance between the two nitrogen atoms of tubocurarine is 12.5 A° and not 14. Tubocurarine causes a longer lasting blockade than decamethonium, the ten carbon poly-

methylene derivative, which has an inter-nitrogen distance of 14 A°.

THE METHONIUM DERIVATIVES

It seems that curaremimetic activity is optimal when methyl substituted quaternary bases are separated 12–15 A° apart. A series of polymethylene bis trimethyl ammonium salts whose chain length varies from two to eighteen carbon atoms has been prepared and their pharmacologic effects studied. The generic term *methonium* is used to designate these straight chain compounds. In this series the Greek prefix (deca, hexa, etc.) placed before the word methonium designates the number of carbon atoms intervening between the two nitrogen atoms. The term "*bis*" placed before the name of the compound refers to the fact that two nitrogen atoms are present on the molecule. The better known compounds in this series are *bis-pentamethonium, bis-hexamethonium* and *bis-decamethonium* (Table II.23). These are often referred to as C5, C6 and C10 respectively. In addition to varying degrees of autonomic, ganglionic and muscle blocking activity methonium compounds exert a muscarine-like effect, a stimulating action on smooth muscle, an ability to contract skeletal muscle directly, an anti-acetylcholine esterase activity and even an anti-bactericidal action. The potency, selectivity of action and the multiplicity of pharmacologic effects is determined by the length of the carbon chain. The 10 carbon compound is the most potent as far as neuromuscular blocking activity is concerned. Ganglionic blocking effects are most pronounced with the five and six carbon compounds. Compounds with 12 carbon atoms appear to exert the greatest muscarinic activity. Those with eighteen car-

TABLE II.23
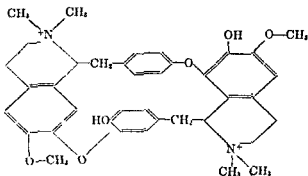
d. Tubocurarine
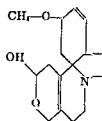
Dihydrobeta erythroidine
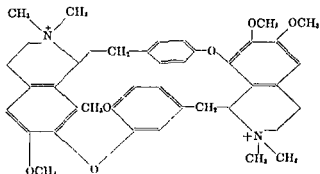
Dimethyl Tubocurarine (Metubine)
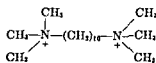
Decamethonium (Syncurine)
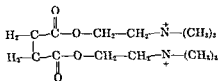
Succinyl Choline
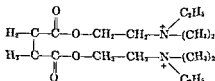
Suxethonium (Brevedil)
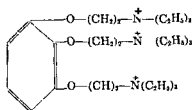
Gallamine (Flaxedil)
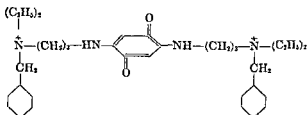
Benzoquinonium (Mytolon)
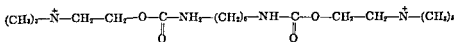
Hexabiscarbacholine (Imbretil)

(Continued on next page)
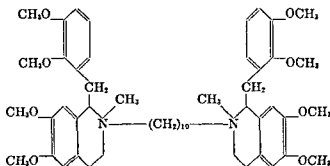
Laudexium

bon atoms seem to have the greatest surface tension effect.

The total number of carbon atoms is not the dominant factor in determining pharmacological activity unless it relates to the inter-quaternary distance. The total number of carbon atoms in tubocurarine exceeds ten, numbering 20, yet the inter-nitrogen distance is only 12.5 A°. The carbon atoms in tubocurarine are arranged in a cyclic fashion. A 6 carbon ring may actually separate the atoms the distance of three carbon atoms in a chain. Thus, even though there are more than ten carbon atoms in the numerous complex alkaloids found in the curares the rings maintain the quaternary nitrogen atoms at the optimum distance.

Other synthetic muscle relaxants not of the methonium type have the same characteristics in regards to possessing two quaternary nitrogen atoms. The more important of these are benzoquinonium (Mytolon), succinyl choline, suxethonium and laudexium (laudolissin) (Table II.23). The inter-inter-nitrogen distance in these, likewise, varies from 12 to 14 or 15 A°, even though the carbon atom arrangement is not necessarily a straight chain. However, if their molecules are visualized in a three dimensional plane it is possible to conceive that the inter-nitrogen distance is 15 A°. Laudexium, which has the nitrogen atoms attached

to cyclic structures are separated by a decamethylene chain. These substances are discussed individually later. The greatest potency is most frequently associated with mono and di-quaternary compounds, however. The presence of more than two nitrogen atoms appears to reduce curaremimetic activity. There are exceptions, however. Gallamine is a tri-quaternary base; yet it is remarkably potent.

NON-QUATERNARY CURAREMIMETICS

Exceptions may also be cited to the generalization that the curaremimetic activity is associated with quaternary bases. A number of non-quaternary alkaloids exist which possess curaremimetic activity. Erythroidine, an alkaloid in Erythrina Americana, is curaremimetic in spite of the fact that it possesses a single tertiary amino group and no quaternary ammonium nitrogen. Conversion of a quaternary base to an amine nullifies its curaremimetic activity. Conversion of an amine to a quaternary base confers upon a compound certain degrees of curaremimetic activity. Quaternary derivatives of quinine, pyridine, isoquinoline and various tropine alkaloids manifest curaremimetic activity.

CHANGES IN THE MEMBRANE AT THE MOLECULAR LEVEL

Although considerable data has been

accumulated concerning the makeup and behavior of the post-junctional membrane, little is known concerning its chemical components and how they are arranged. Ample data relating to the electrical capacity, thickness, impedance, rate of polarization and depolarization of the membrane are available. The changes occurring at the molecular level during repolarization and depolarization at the time of this writing remain virtually unknown, however. The chemical nature of the cholinergic receptors at the end plate is unknown. How these receptors are altered by acetylcholine, the muscle relaxants and other agents, likewise, is not understood. Recently workers in this field have been employing agents labeled with radioactive isotopes for studying the behavior of relaxants at the membrane. Non-depolarizing drugs have been labeled with C^{14}; depolarizing drugs with C^{14} or I^{131}. Tubocurarine may be converted to the dimethyl ether which is then tagged with radioactive methyl iodide. Methylated curarine and gallamine tri-iodide may be tagged with radioactive iodine. Decamethonium may be tagged with C^{14}. With these techniques it has been possible to obtain some data on the locus of action, the diffusion itself and changes in concentration at various sites.

BONDING OF THE RELAXANT AT THE RECEPTOR

It has been determined, by using isotopes, such as these, that the combination which occurs between the relaxant and the receptor in the membrane is due to ionic bonding. Whatever combination occurs is reversible and undergoes dissociation. This it would not do if the union were by covalent bonding. A positive ion is invariably associated

with neuromuscular blocking activity. It has been proposed that the mechanism may be similar to the one which takes place in an ion exchange resin arrangement. In such an arrangement the resin holds, by ionic bonding, a particular ion. This ion can be exchanged for another of like charge which is present in the media surrounding it. The electrical polarity of the nucleus of the exchange resin remains the same. The ion which is exchanged has the same charge as the one which is displaced. The quaternary basic ion is exchanged for another ion of similar charge, possibly potassium. Tubocurarine produces no detectable electrical disturbance when applied to the end plate with a micropipette. This behavior strongly suggests that an exchange process occurs.

CHEMICAL NATURE OF THE RECEPTOR

Studies using radioactive isotopes also reveal that drugs so labeled are found to non-diffusable macro-molecular components. There appears to be a preferential uptake of quaternary bases at the end plate. Heretofore, it was assumed that the receptor substances were proteins. Recent data indicates that this may not be so and that the receptor may be a complex amino polysaccharide. Evidence also exists that the tissues contain negatively charged substances which are capable of binding positive quaternary ammonium ions. The strength of the bond between the ionized relaxant and the receptor is unknown. Whether or not some relaxants are held more firmly than others is not definitely known.

DISTRIBUTION AT THE END PLATE

The rate of curarization and recovery is influenced by the ability of the various drugs to diffuse in and out of the re-

ceptor substance. The plasma concentration reaches its peak within several minutes after an intravenous administration of a muscle relaxant. The relaxant then diffuses from the plasma to various parts of the extracellular fluid compartment. Quaternary bases unlike amines penetrate epithelial barriers with difficulty. For this reason they are poorly absorbed. They penetrate the neuromuscular membrane with ease, however. The end plate has a higher content than any other tissue after injection is complete. A distribution equilibrium is ultimately established between the vascular space and extracellular fluid compartments. Paralysis develops when the concentration necessary to produce a block penetrates the membrane at the end plate. The fraction of the relaxant taken up by the end plate is quickly adsorbed to the receptor substance. The maximum tissue concentrations in other parts of the extracellular compartment are reached much later than at the end plate. They vary for each relaxant. Maximum tissue (other than neuromuscular) concentrations of d-tubocurarine are not reached for at least an hour, even though paralysis becomes established within four minutes and is over within twenty. Little of the d-tubocurarine is excreted or decomposed in the body while the block is in progress. The drug is not destroyed at the receptor site. The neuromuscular block, therefore, is terminated by a re-entry of the drug from the end plate into the plasma. This comes about when the concentration of muscle relaxant in the plasma is reduced by excretion, decomposition, hydrolysis or storage in other tissues. The drug is still present in the plasma but at lower concentration than at the end plate but at a higher one than in other tissues. The drug, there-

fore, continues to pass into these tissues where it causes no physiological change.

EFFECT OF BLOOD FLOW

The degree of curarization not only varies with the distribution, excretion and metabolism of the relaxant but also with the state of the curarization, degree of hydration, electrolyte balance, body temperature and so on. The end plate is well supplied with blood. Increasing the blood flow increases the rate of onset of the blockade and rate of recovery from a muscle relaxant. Vasoconstriction caused by cold slows the onset and prolongs the duration in the case of both depolarizing and non-depolarizing drugs. Tubocurarine and most "onium" compounds are stable in all tissues including muscle tissues. They are not easily destroyed by oxidation or hydrolysis. They pass through renal epithelium with more ease than they do other areas. Therefore, a greater portion of a given dose is found unchanged in the urine.

EFFECT OF MOLECULAR SHAPE

Curaremimetic substances have been classed by Bovet as *pachycurares* and *leptocurares* according to their molecular bulk. The molecules of the leptocurares are relatively slender compared to those of the pachycurares. The latter have a broader molecule due to the pressure of cyclic groups. The leptocurares, therefore, diffuse readily through the membrane into the muscle fibre in contradistinction to the pachycurares. They act like acetylcholine and depolarize the membrane. Succinyl choline and decamethonium have slender molecules of small diameter and are, therefore, leptocurares. Tubocurarine, laudixium and gallamine are pachycurares. The quaternary nitrogen atoms are

separated by cyclic structures which are responsible for the broad molecule. They remain outside the membrane and become attached to the cholinergic receptors thereby interfering with the depolarizing effect of acetylcholine. Depolarization type of block is more frequently associated with the leptocurares while non-depolarizing block is observed more frequently with the pachycurares. This difference in molecular configuration may help explain the marked species variations encountered with the relaxants. A given compound may produce a depolarizing block in one species and an anti-depolarizing block in another. The behavior of the pachycurares is more uniform and less subject to the various species variations. More variations in behavior are found among the leptocurares. Tubocurarine does not readily penetrate into the muscle fibre. Tubocurarine inhibits contraction when introduced directly into the muscle fibre with a micropipette technique. It then produces a depolarizing type of block. Ordinarily it is found bound to the receptor at the surface of the cell where its action is of the non-depolarizing type only. Decamethonium, on the other hand, penetrates into the cell and causes depolarization.

VARIATIONS IN TYPES OF MUSCLE

Another factor responsible for the variability of data obtained in studies of neuromuscular block is that curaremimetic activity varies according to the type of muscle being studied. Some muscle fibres are innervated by small nerve fibres and some by large. The response to relaxants varies with the two types using the same drug in the same species. The rectus abdominus of the

frog, for instance, is innervated by the small type nerve fibres. A tetanizing effect results when muscle fibres of this type are treated with acetylcholine. The sartorius muscle in the same species, on the other hand, is innervated by larger fibres. It responds to acetylcholine with a single twitch. Red muscle and white muscle are also affected in different ways. In the cat white muscle is more sensitive to decamethonium than red. The chemical significance of this has not been established.

ANTI-CURARE ACTIVITY

The junctional membrane fails to repolarize if acetylcholine accumulates at the end plate. Certain substances, referred to as *anti-cholinesterases*, inhibit the hydrolytic action of acetylcholine esterase thereby causing acetylcholine to accumulate at the end plate. The accumulated acetylcholine, in accordance with the mass action law, displaces the relaxant from the receptor and re-establishes transmission. Anti-cholinesterases may, therefore, be of value as antagonists to non-depolarizers. Other quaternary bases, such as decamethonium and succinyl choline depolarize the junctional membrane in the same manner as does acetylcholine. The initial response on contact with the junctional membrane is an excitation which causes a twitch of the muscle fibre similar to that produced by acetylcholine. These substances remain in contact with the membrane longer than acetylcholine or they penetrate into the cell. Their destruction or removal is much slower than that of acetylcholine. Therefore, after the excitation a flaccid state of the muscle develops which persists for a longer period of time than it does with acetylcholine.

Protection of acetylcholine by anti-cholinesterases results in an additive effect and enhances the depolarizing effect of these drugs. Therefore, anti-cholinesterases extend the action of drugs such as decamethonium, succinyl choline and other non-depolarizers.

The best known of the anti-cholinesterases are eserine (physostigmine), neostigmine and edrophonium (Tensilon) (Chap. 22). Eserine is a tertiary amine while neostigmine and edrophonium are quaternary bases. They differ in their molecular configuration from the relaxants in being aromatic compounds. Alkyl esters of phosphoric acid, as for example, hexaethyl phosphoric acid also possess anti-cholinesterase activity. It is believed that their action is irreversible because they act by phosphorylating the enzyme by attachment of an alkyl phosphate radical by a strong covalent bond. Eserine, edrophonium and neostigmine do not. The types of and mode of action of the anti-cholinesterases are given in more detail in Chapter 20.

Anti-cholinesterases fail to reverse the action of non-depolarizers at times. There are a number of reasons why this occurs. Tubocurarine antagonism is maximal when an anti-cholinesterase completely inhibits the enzyme. Increasing the concentration of anti-cholinesterase beyond this point is of no benefit. In fact it may be detrimental if the anti-cholinesterase is a quaternary base because it may augment the action of tubocurarine. The end plates may lose their sensitivity to acetylcholine in which case transmission is not re-established. An excess accumulation of acetylcholine may result and produce an acetylcholine block. A slowly reversible or pathological fixation at the end plate may also result in failure of the drug to act. Cooling antagonizes non-depolarizing block by increasing the activity of acetylcholine, while it does not influence depolarizers in this regard.

EFFECT OF ELECTROLYTES

Sodium and potassium ions are found in myoneural tissues. Sodium is found mostly in the extracellular tissues; potassium in the intracellular. Neuromuscular activity is associated with inward diffusion of sodium and outward diffusion of potassium. At rest the concentration is maintained despite the gradients which are established by each ion on their respective sides of the membrane. Addition of potassium chloride to a muscle nerve preparation results in depolarization and contraction.

Potassium

The potassium ion, therefore, would be an antagonist to tubocurarine. However, it is not used clinically because it causes undesirable side effects in addition to the antagonism. The depolarizing effect of the end plate potential by potassium is exerted largely on the membrane. Epinephrine causes an increase in potassium which may cause antagonism to curare. Potassium ion also causes changes in other parts of the muscle fibre which are not fully understood. An excess of potassium ion also causes the liberation of acetylcholine which also antagonizes the tubocurarine.

Sodium and Calcium

A decrease in sodium ion concentration at the end plate reduces the size of the end plate potential. The results obtained may be due to alterations beyond the membrane also. Lowering the calcium ion concentration also decreases the end plate potential.

Calcium and Magnesium

The decrease in calcium ion concentration is followed by a decrease in acetylcholine output at the nerve ending which in turn causes irritability of the post-junctional membrane and spontaneous depolarization. This results in tetany. An alkalemia of sufficient intensity to cause a decrease in calcium ions does likewise. An increase in calcium has a stabilizing effect on the membrane and prevents the depolarization effect of potassium ions. Presumably the calcium causes an increase in acetylcholine production at the nerve endings which in turn causes the stabilization. A decrease in calcium makes the membrane more labile to the effects of potassium. An increase in magnesium causes a neuromuscular block. Magnesium and calcium ions are mutually antagonistic. The effects of the magnesium ion are additive.

Combination of Ions

A deficiency of all three ions, potassium, sodium and calcium, retards transmission and enhances the effects of nondepolarizers. Sodium and potassium ions antagonize d-tubocurarine. The antagonism caused by potassium is enhanced by decreasing the temperature and the post-junctional area. It is also counteracted by anti-cholinesterases. Dehydration may enhance the effects of muscle relaxants by causing imbalances in electrolytes and shifts of ionic concentrations. Disturbances in renal function allow the various cations to accumulate, thereby influencing neuromuscular block. Osmotic diuresis increases the excretion of the ions and augments the action of the relaxant. A potassium ion deficiency resulting from imbalances of electrolytes may enhance the relaxant effect.

ELECTRICAL CURRENTS

The application of a cathodal current to the end plate decreases the depolarizing effect. This resembles the application of potassium. An anodal current hyperpolarizes the membrane and increases the intensity of a nondepolarizing block.

COMBINATION OF MUSCLE RELAXANTS

Combining relaxants may cause either an antagonism or an enhancement of the relaxing effect, depending upon the type and the sequence of administration of each with reference to the other. Tubocurarine tends to overcome the depolarization caused by decamethonium by reducing the end plate potential. In animals decamethonium is less potent after the administration of tubocurarine. The reverse process, that is, the antagonism of tubocurarine by decamethonium is not demonstrated as easily. The explanation offered is that decamethonium not only depolarizes the motor end plate but enters the cell and causes a depolarization in the area adjacent to the membrane within the muscle fibres.

BIPHASIC ACTION OF DEPOLARIZERS

Depolarizing agents such as decamethonium and succinyl choline act in a biphasic manner. Patton and Zaimis first demonstrated that decamethonium caused a sustained block at the end plate. A rapid succession of nerve impulses no longer produced an end plate potential and the muscle did not contract. The drug rendered the muscle inexcitable not only at the end plate but beyond the plate for a distance of 2–3 mm. from the junctional membrane. Later it was shown that the block caused by decamethonium is a biphasic affair. The first phase is the one which is char-

acterized by depolarization of the end plate. This causes a twitch of the muscle which is followed by recovery of the potential on the membrane. Recovery of the membrane occurs even though the drug is still present in the receptor. Later a non-depolarizing block follows which resembles that produced by tubocurarine. This is due to the fact that decamethonium enters the muscle fibre and a difference in concentration develops between the inside and the outside of the fibre. The accumulation of the drug inside has an anti-depolarizing influence. The membrane which is depressed in the first phase recovers in the second. Tubocurarine introduced into the muscle cell with a micro-pipette produces a depolarizing block also. Tubocurarine, however, does not depolarize the end plate. The tubocurarine probably cannot, under ordinary circumstances, depolarize the end plate because it lacks the power of penetration which apparently is possessed by decamethonium. This behavior of decamethonium to cause depolarization which is followed by repolarization possibly explains the tachyphylaxis occasionally seen in certain individuals when depolarizing agents are used. Apparently they do not enter the fibre and, after depolarization of the first phase has disappeared, the membrane is restored to activity. The reversal of the block by depolarizers when followed by antagonists after prolonged use of the drug may also be explained by the fact that the second phase is a non-depolarizing block. It also explains the failure of antagonists to act in certain cases of overdosage because both a depolarizing block and non-depolarizing block are present. Unfortunately all that goes on at the end plate is not easily explained. More can be explained con-

cerning the action of non-depolarizers than depolarizers.

HISTAMINE RELEASE

Histamine exists in a bound state in the body. Part of it appears to be bound with proteins in the mast cells which are widely distributed in the body. These cells are perivascularly located. The cells are abundant in the skin. The mast cells lose their basophilic granules and become distorted as the histamine is released. In addition a large store of tissue histamine is found in the body not associated with mast cells. This fraction is not readily released unless serious tissue damage is induced. Many organic bases mobilize histamine by releasing it from its bound state.

Most muscle relaxants are histamine-liberators. Previous sensitization by the drug is not necessary for this release. The exact mode by which this release comes about is not known. Possibly it is due to an ion exchange process in the mast cells which causes release of histamine, or the binding agent competes for the liberator or to activation of mast cell lecithinase by interfering with a normal inhibitor. All muscle relaxants so far studied exhibit a histamine release phenomenon. However, the fact is of little consequence because the dose required to effect the release is large in comparison to that required for neuromuscular blockade. Besides most anesthetics inhibit the release. The most important relaxant which manifests any remarkable degree of histamine release is d-tubocurarine. Large doses of succinyl choline could possibly release histamine but ordinarily little is released since the drug is broken down rapidly. It, thus, plays a minor role in this regard. Histamine release is not a major clinical problem.

INDIVIDUAL DRUGS

CURARE AND TUBOCURARINE

Curare is not a specific compound. Instead it is a mixture of various substances obtained from numerous botanical sources most important of which are the Strychnos and Chondrodendrons. Extracts of herbs from these plants are referred to as curare. There are, therefore, various curares depending upon the botanical source and the proportion of the herbs from which the mixture is made. Crude curare contains a number of chemically related alkaloids with closely related pharmacological actions. Formerly curares were classified according to the type of containers the natives used for curare. Such terms as "tube" curare, "calabash" curare and "pot" curare gave no indication of the composition of the crude drug.

CURARE EXTRACT

Prior to the isolation of the alkaloid the extract obtained from Chondrodendron tomentosum was used almost exclusively for clinical purposes. Chondrodendron tomentosum extract (Intocostrin) is a purified preparation containing the therapeutically desirable constituents of crude curare (Tubocurarine). In the preparation of the extract the barks and stems of the plant are first steeped with water and then with alcohol. The extracts are combined and then evaporated to dryness after which the residue is re-dissolved in water and the pH is adjusted to 4.6–4.8 with hydrochloric acid. The preparation is standardized biologically in rabbits using the head-drop, cross-over technique. One unit represents the quantity of active principles necessary to cause paralysis of the neck muscles per kilogram of rabbit. The extract is available in a sterile aqueous

solution in 10 ml. vials. One ml. of the purified extract contains 20 units of active alkaloids. The curariform activity of the extract is due almost entirely to the tubocurarine content. One unit of active principle has a potency equal to that of 0.15 mg. of d-tubocurarine chloride pentahydrate. The solution is stable under ordinary conditions of storage (25°C. and sealed).

TUBOCURARINE

The crystalline alkaloids of curare were first isolated by Pia in 1846. The structure of d-tubocurarine was first established by King in 1936. Later Wintersteiner and Dutcher (1943) isolated a substance from crude curare prepared from Chondrodendron tomentosum having a structure identical to that described by King.

D-tubocurarine is a di-quaternary ammonium base, that is, it has two quaternary nitrogen atoms. The alkaloid has a complex structure consisting of a double tetra hydro-isoquinoline nucleus. These rings are held apart by two benzine rings (Table II.23). The nitrogen atoms are in the ring but are separated for a distance of 12.5 A° by virtue of these heterocyclic structures. No straight chain separates the nitrogen atoms. The structure of tubocurarine as is the case with other important curaremimetic compounds (with the exception of decamethonium), contains oxygen in addition to carbon, hydrogen and quaternary nitrogen. Four oxygen atoms are present—two as hydroxyl groups and two as ether groups. The isoquinoline nuclei are attached to supporting benzine rings by two methylene linkages and the two ether linkages. The methylene and ether linkages are inert. The quaternary nitrogen

atoms are on opposite sides of the molecule.

Properties

Two optical isomers are possible. a dextro and a levo. The levo compound is less potent than the dextro. The active isomer has a specific rotation of $[\alpha]_D^{22}$ + 215° The drug (pentahydrate) is a white or yellowish white powder which melts at 270°C. Aqueous solutions have a pH of 3.0. One gram dissolves in 20 ml. of water and 45 ml. ethyl alcohol. The drug is insoluble in ethyl ether, chloroform, benzine, pyridine and acetone.

Solubilities

Tubocurarine forms a number of hydrates. An anhydrous form may be prepared which is markedly hygroscopic and absorbs water until it reaches the pentahydrate state. The pentahydrate seems to be fairly stable and non-hygroscopic. Super saturated solutions of d-tubocurarine are possible due to hydrate formation. The solubility is reduced by acids. Tubocurarine, since it is a di-quaternary base, interacts with two molecules of hydrochloric acid to form a hydrochloride. The reaction is similar to that which occurs when ammonium hydroxide interacts with the acid to form ammonium chloride. Solutions ionize to a quaternary ammonium cation which presumably is the physiologically active form of the drug. Tubocurarine is difficult to obtain in an absolutely pure form because it is obtained from natural sources and, therefore, contains contaminating alkaloids which are difficult to separate completely. These may be demonstrated by paper chromatography. The drug, therefore, is bioassayed in the same manner as the extract by the head-drop method to assure standard potency. It is packaged in vials

containing 10–20 ml. of sterile 0.3% aqueous solution. Each cubic centimeter of the solution contains 3 mg. of dextrotubocurarine chloride pentahydrate or, in other words, 20 units of activity. A high potency solution is also available in a 15 ml. ampule. Each ml. contains 15 mg. or 100 units of the alkaloid. This is for use with barbiturates. Occasionally tubocurarine and a barbiturate are mixed and injected simultaneously. The sodium salts of barbituric acids when dissolved in water have a pH between 11 and 12. On the other hand tubocurarine produces an acid solution. Consequently if sufficient tubocurarine chloride is added to the barbiturate solution to produce an acid solution the acid form of the barbiturate forms. The barbituric acid is less soluble than the salt and, therefore, precipitates out. The degree of precipitation depends upon how acid the mixture becomes. As a rule, a compatible mixture contains 33 milligrams of thiopental to one of d-tubocurarine chloride.

Absorption of Curare Alkaloids

Tubocurarine is not absorbed from the unbroken skin. It is inactive when administered orally, unless large doses are administered. Presumably the drug is inadequately absorbed through the gastro-intestinal tract or it is destroyed on its passage through the mucosa. Quaternary bases, as a rule, are poorly absorbed through mucous membranes. Tubocurarine is absorbed from muscular sites after hypodermic administration. However, the onset of action is not as rapid as it is after intravenous injection.

Distribution in Tissues and Fate

Tubocurarine, as are most related

muscle relaxants, is hydrophilic rather than hydrophobic or lipophilic. Therefore, it is uniformly distributed in the body tissues. Kalow has noted that the passage of tubocurarine through the body may be divided into three distinct phases. In the first phase, during which the plasma level is reduced by one-half within 5–6 minutes, distribution is throughout the extracellular fluid. During this time the drug passes into the end plate. Some binding with plasma proteins occurs in this phase. During this phase the lowering of plasma level is due to dilution in the total water of muscle and other organs. In the second phase the drug disappears from the extracellular fluid. Most of the disappearance is due to urinary excretion and passage into some cells. This phase has a half time of 45 minutes. In the third phase, which requires 3½ hours, the drug which has passed into the cells is destroyed by enzymes or eliminated unchanged. Enzymes capable of destroying drugs are located in the microsomes which suggests that the drug passes into some of the cells. About ⅔ of a given dose appears to be destroyed. The rate of destruction is slow. Renal excretion plays the major role during the phase in which the drug is passing into the cells. During this time about ⅓ of the drug is being excreted in the urine. In man about ¾ of a dose of d-tubocurarine is recovered in the urine over a period of several hours, irrespective of the route by which the drug is administered. Tubocurarine does not enter the red cells to any great extent. Quaternary bases do not appear to penetrate the blood brain barrier, since they are not lipophilic. The duration of action of d-tubocurarine is brief, since it quickly enters the end plate and then leaves it when the plasma level falls. This brevity of action, therefore, is due to the re-distribution of the drug from one tissue to another. Repeated doses produce a cumulative effect since it is stored in the cells and slowly destroyed. Metabolites may be isolated from the urine which indicate destruction has occurred.

DERIVATIVES OF TUBOCURARINE

D-tubocurarine has two hydroxyl groups, both on aromatic nuclei which, of course, confer properties of a phenol to the compound. Each of these is convertible by alkyl groups to form ether linkages (Table II.23). Methylation converts tubocurarine to a dimethyl ether. The dimethyl derivative (dimethyl tubocurarine) is approximately three times as potent but somewhat shorter acting than d-tubocurarine in man. The pharmacological properties are similar to those of d-tubocurarine. The dimethyl derivative also forms salts with acids. The principal salts are chlorides and iodides. The iodide (Metubine) is a white, pale, yellowish, odorless, crystalline powder. The drug is dextrorotatory $\alpha_D^{22°} = +148$–158. It decomposes with the evolution of gas when heated to 257°C. It is slightly soluble in water, dilute hydrochloric acid and dilute sodium hydroxide. It is very slightly soluble in alcohol and practically insoluble in benzine, chloroform and ether. The chloride is employed clinically when iodism is feared (Mecostrin). The pH of the aqueous solution is 6.1. Approximately 0.8 mg. of the chloride is employed for every milligram of the iodide because of the differences in molecular weight. The methyl ether is made directly from d-tubocurarine. Both drugs are stable in solution. The urinary excretion is greater than that of d-tubocurarine. More than 55% is recovered in the urine.

The substitution of the methyl groups on the quaternary nitrogen atoms of d-tubocurarine and its allies by other groups diminishes muscle relaxing effects. Replacement of the methyl groups by hydrogen atoms completely nullifies the relaxant effects.

CHONDROCURARINE

A substance closely allied to d-tubocurarine, known as d-chondrocurarine, has a somewhat similar structure, the chief difference being a change in the position of one of the hydroxyl groups for one of the methoxy groups. Besides the quaternary amino alkaloids, alkaloids with tertiary amino nitrogens combined with quaternary nitrogens are found in curare also. These are known as curarines and are found in Chondrodendron tomentosum.

Methods of Detection

Tubocurarine responds to tests characteristic of phenols, quaternary bases and ethers since these groupings are present on the molecule. D-tubocurarine and related compounds react with Millon's reagent. This test detects the presence of the hydroxyphenyl or phenol group. A green color develops with ferric chloride, indicating that a hydroxyl group is present on a benzine ring. None of these reactions are specific for the alkaloid alone, however. Pride and Smith have suggested the use of Millon's reagent for the determination of the drug but the method is not used.

A number of techniques have been suggested for the qualitative and quantitative determination of the alkaloid which tend to be more specific. The Council on Pharmacy and Chemistry suggests that the optical rotation be used for assay and for determining the purity

of the drug. Relatively concentrated solutions are required to obtain reliable results by this method, however. The specific rotation of the hydrate is +190 at 25°C. using a sodium light. The melting point may also be used for identification. Optical rotation and melting point alone are not sufficient for identification and assay of a drug. D-tubocurarine chloride melts at 272-273°C.

The biological method of assay is used for standardization as has been mentioned previously. The colorimetric method using a choline-phenol reagent has been suggested also. A polarity method procedure has been described by Foster. Kline and Gordon have suggested the use of the spectrophotometric absorption in the ultra-violet light region. The alkaloid is extracted after alkalinization of the solution with ethylene dichloride. The salt is then reformed by the addition of 0.1N HCl. The spectrophotometric absorption of the Reineckate* in the visible region is also suggested. A study of the ultra-violet absorption curve of the salt and aqueous solution indicates that absorption is maximal at 2A-281 mμ. D-tubocurarine chloride forms an insoluble Reineckate.* This salt is dissolved in alcohol and estimated colorimetrically at 525 mμ.

SUCCINYL CHOLINE

HISTORY

Succinyl choline (Anectine, Quelcin, Sucostrin) was known for a number of years before its muscle relaxing qualities were discovered. As early as 1911 Hunt and Taveau studied its pharmacological effects in animals. Its relaxant effects, however, were overlooked because they studied the drug in curarized

* Ammonium tetrathiocyanodiammonochromate

animals. It was not until 1949 when the muscle relaxant effects were discovered by Bovet and his co-workers in Italy.

SYNTHESIS

Studies of the methonium compounds indicated that a pair of carboxy groups introduced into a polymethylene bis-methonium chain lessened the duration but not the intensity of muscular relaxing activity. This led to the synthesis of succinyl choline. The drug is synthesized by refluxing diethyl succinate with beta-dimethyl-amino ethanol and forming bis dimethyl amino ethyl succinate. Interaction of this product with methyl iodide forms succinyl choline.

PROPERTIES

Succinyl choline is a quaternary base with two nitrogen atoms separated from each other by a distance equivalent to ten intervening atoms (Table II.23). The structure, therefore, if visualized in a chain-like arrangement, is long and slender like decamethonium and not broad like tubocurarine. The "onium" groups are sufficiently basic to form salts with acids. The salts dissociate and react with water to give acidic solutions. The cations are physiologically active and presumably interact with the receptors. Succinyl choline chloride is also known as diacetyl choline chloride. Actually the compound is two molecules of acetylcholine linked together at the alpha methyl groups.

Succinyl choline is a white, odorless, slightly bitter powder which forms a monohydrate. The hydrate melts at 156–160°C. It is very soluble in water (1 gm. per ml.) alcohol (1 gm. in 350 ml.), slightly soluble in benzine and chloroform and practically insoluble in ether. The pH of a 2% solution varies between 3.0–4.5. Two

salts are available for clinical use—the chloride and the iodide. The chloride is preferred to the iodide since the latter may cause iodism. The ratio of the molecular weights of succinyl choline chloride and iodide is 1:1.5. Therefore, the equivalent dose of succinyl choline should be calculated as % of the iodide.

STABILITY

Succinyl choline chloride powder is relatively stable and may be sterilized by autoclaving. However, it is best stored under refrigeration. The potency of solutions exposed at room temperature gradually decreases. Biological assay, however, shows that solutions may be kept for as long as three months at room temperature without significant loss of potency. Alkalies hasten their decomposition.

Succinyl choline may be assayed by refluxing it with sodium hydroxide and determining the amount of succinic acid released by titrating the unneutralized sodium hydroxide with 1/10 normal hydrochloric acid.

Succinyl choline is rapidly hydrolyzed in alkaline solution in vitro. It differs from other relaxants in this respect. It is, therefore, incompatible with solutions of sodium salts of the barbiturates, such as thiopental or thiamylal.

METABOLIC FATE

Succinyl choline is hydrolyzed by the pseudocholinesterases of the plasma. The products of hydrolysis are succinic acid and two molecules of choline. Both succinic acid and choline occur normally in the body as metabolites. The hydrolysis by the esterase occurs rapidly and completely. Not more than 2% of an injected dose appears in the urine. The serum cholinesterase acts only while the

drug is in the serum. The succinyl choline must leave the plasma in order to reach the receptors in the myoneural junction. The hydrolysis leads first to the formation of succinyl monocholine and choline. This reaction occurs rapidly. The monocholine follows at a much slower rate—approximately 6–8 times more slowly. The liver contains an esterase which is believed to be specific for succinyl monocholine. Therefore hydrolysis does not depend upon the cholinesterases alone.

Succinyl choline is not hydrolyzed by the true cholinesterase found in the red blood cells and that in the end plate region. The monocholine exerts an inhibitory effect on pseudocholinesterase and, therefore, retards hydrolysis of succinyl dicholine. Succinyl choline and its derivatives also exert an inhibitory effect on the hydrolysis of acetylcholine by true cholinesterase. The average rate of hydrolysis of succinyl choline is about 3 micromoles per ml. of plasma in 30 minutes.

The pseudocholinesterases are widely distributed in plasma and other body fluids. At least three different types have been differentiated by the technique of determining inhibition by dibucaine. There appears to be two types in man in regards to succinyl choline hydrolysis—a typical one and an atypical one. Approximately 97% of the population have the typical form which readily hydrolyzes succinyl choline. Approximately 4% have a mixture of both types while 1 in 2800 persons has the atypical type. The typical esterase is very active at concentrations of succinyl choline which are too low to induce activity of the atypical enzyme. Succinyl choline exerts its effect for a much longer period of time in a person with atypical esterases.

Prolonged apneas have occurred after the use of succinyl choline. The exact explanation for this is not known. Failure of the esterases to hydrolyze the succinyl choline has been presumed to be a factor. It is difficult to prove that the esterase was acting effectively during the apnea even though in vitro studies show an active esterase. The enzyme may be inhibited in vivo by drugs and other agents while in vitro these inhibitors are diluted out or inactive. A lowering of esterase levels occurs in liver disease, malnutrition and cachexia due to failure of protein synthesis. A decrease of esterase activity possibly combined with electrolyte disturbance may be responsible for the apnea. Blood and tissue levels of succinyl choline are difficult to determine.

Succinyl monocholine also produces a depolarizing block, but somewhat weaker than that of the dicholine. The potency on a milligram for milligram basis is 1/20 that of succinyl choline. The block caused by the monocholine is longer lasting. The possibility of accumulation of the monocholine when succinyl dicholine is given by the intravenous drip must be borne in mind. Cooling tends to increase the duration and magnitude of the depolarizing block produced by succinyl dicholine.

The hydrolysis of succinyl choline is accelerated in an alkaline medium. It is rapid at a pH of 7.4. Respiratory alkalosis accelerates the hydrolysis. However, this is not a potent factor in destruction. Less than 5% per hour of the succinyl choline in the body is destroyed by alkaline hydrolysis. Alkaline solutions are incompatible with succinyl choline. Solutions of barbiturates, therefore, cannot be mixed with the drug since they have a pH of 10–12.

MISCELLANEOUS CHOLINES

Other cholines have been prepared with muscle relaxant properties. Among these are Brevidil which has one ethyl group replacing one methyl on each nitrogen atom of succinyl choline.

DECAMETHONIUM

STRUCTURE AND SYNTHESIS

Decamethonium is the simplest, structurally speaking, of the commonly used neuromuscular blocking agents. It consists of two quaternary nitrogen atoms separated by an intervening aliphatic chain of ten carbon atoms (Table II.23). This chain is often referred to as the decamethylene chain. No oxygen or atoms of other elements save hydrogen are present on the aliphatic chain. The decamethylene chain is relatively inert. The drug, therefore, is very stable in solution. Decamethonium may be synthesized by treating decamethylene bidiamine in methyl alcohol solution with methyl bromide and sodium hydroxide. Sodium bromide forms as a byproduct which is removed by extraction with acetone in which the decamethonium is insoluble. As is the case with other quaternary bases decamethonium forms salts with acids. These dissociate in aqueous solutions to form a nitrogen containing cation which is responsible for the physiological effect.

PROPERTIES

Decamethonium is available under the trade name of Syncurine. It is also called C-10. The drug is a white crystalline, water soluble powder. It is soluble in alcohol but insoluble in acetone. The initial effect is one of depolarization. A sterile solution contains one milligram of the salt per milliliter. The solution is stable and non-irritating to the tissues. The drug is compatible with barbiturates in the same solution. Decomposition of the salt occurs at 252°C.

DISTRIBUTION

As is the case with other quaternary bases, decamethonium is poorly absorbed after oral ingestion. The compound is distributed in the extracellular fluids and like other quaternary ions penetrates the body cells slowly. There is little or no destruction of the drug in the body. The drug is quantitatively and almost completely excreted in the urine unchanged (up to 90%). Elimination occurs through the kidney, presumably by filtration by the glomerulus. Patients who have renal insufficiency may retain the drug and manifest cumulative effects.

HEXA-BISCARBOCHOLINE (IMBRETIL)

STRUCTURE AND SYNTHESIS

Hexa-carbabischoline is a hexa methylene (6 carbon chain) which has an amino group (hexamethylene diamine) attached at each end of the carbon chain (Table II.23). One hydrogen of each amino group is substituted by a tri-methyl carbaminoyl group. The drug is prepared by reacting glycol carbonate with hexamethylene diamine. The hydroxyl groups are then replaced by chlorines by treatment with SO Cl₂. The Cl is then changed to I by treating with sodium iodide. The I is replaced by trimethyl amine to form the hexa biscarbaminoyl choline. The drug contains two quaternary hydrogen atoms separated by a chain of more than 10 carbon atoms. Bends may occur at the nitrogen atoms so that the traditional inter-nitrogen dis-

tance of 14 A° is maintained. The compound is remarkably stable. Heating with NaOH for ten hours fails to hydrolyze the compound. Cholinesterases, in vivo, likewise do not hydrolyze the compound.

BENZOQUINONIUM

PROPERTIES

Benzoquinonium (Mytolon) is a bis quaternary base which possesses the characteristic of both a non-depolarizing and depolarizing blocking agent. The drug was synthesized by Cavallito and his collaborators. The pharmacologic properties of benzoquinonium (Mytolon) were investigated by Hoppe in 1950. The substance is a red crystalline, water soluble material which melts at 191–194°C. The molecule contains two N-benzyl groups which provide the quaternary nitrogen. On these are two ethyl groups. The benzyl groups are attached to propyl amino groups. Each of these is attached on position 3 and 5 respectively of a 1, 4 benzoquinone nucleus (Table II.23). It is available in sterile solutions containing 3 mg. per ml. Solutions are compatible with barbiturates. The compound is excreted by the kidney in an active form which imparts a pink color to the urine. As much as 75% of the drug is eliminated unchanged.

GALLAMINE (FLAXEDIL)

STRUCTURE

Gallamine (Flaxedil) differs from other relaxants in having three quaternary nitrogen atoms. The drug is prepared from pyrogallol (1, 2, 3 trihydroxy benzine). The hydroxyl groups are converted into ether linkages by the attachment of three choline residues to the benzine ring. The structure may be writ-

ten so that two quaternary nitrogen atoms, the 1 and 3 are separated at a distance of 14 A° apart. The 2 substituent is at right angles to the chain. The presence of the third quaternary nitrogen confers greater activity since the 1, 2, 3 derivative is more potent than the 1, 2 or the 1, 3. The 1, 3 derivative which has the nitrogen atoms farther apart than the 1, 2 is the more potent of the two. Another departure from the other muscle relaxants is that the substituents on the nitrogen atoms are ethyl groups instead of methyl. Generally, substitutions of ethyl groups for methyl leads to a loss in potency. The drug is non-reactive and stable in solutions.

As is the case with other quaternary bases the compound forms salts with strong acids which dissociate in water to form acid solutions (pH 3.2). The cations are active physiologically.

PROPERTIES

Gallamine (Flaxedil) is a stable, white odorless bitter powder. It is soluble in water, alcohol and dilute acetone, but insoluble in anhydrous acetone, ether, benzine and chloroform. It is available as a solution; each cc. contains 20 to 30 mg. The substance is not absorbed if administered orally but is effective intravenously. It is compatible with the barbiturates in the same solution. The drug is stable and can be autoclaved at 120°C. The available salt is the iodide which has a melting point of 250°C. Three molecules of hydroiodic acid are required—one for each quaternary nitrogen atom. For this reason Gallamine is referred to as the triodide. Gallamine is well absorbed after subcutaneous administration. The drug is metabolized with difficulty. Up to 100% is found in the urine. The drug acts by competing

with acetyl choline thereby producing a non-depolarizing type of block.

ERYTHRINA ALKALOIDS

SOURCE

The genus Erythrina yields, from its beanlike seeds, substances with curare-mimetic activity. Of 105 known species the seeds of 50 have been shown to contain alkaloids which are physiologically active in regards to muscle blocking effects. Erythroidine, obtained from Erythrina americana, was the first crystalline alkaloid to be isolated. Erythroidine consists of at least two isomeric alkaloids, an alpha and a beta erythroidine. Both are dextrorotatory. The beta form is readily available in the pure state. The erythroidines are exceptions to the rule that relaxants are quaternary bases. They are tertiary amines (Table II.23). Conversion to a quaternary base nullifies the muscle relaxing activity.

POTENCY AND BEHAVIOR

Several hydrogenated derivatives of beta erythroidine have been prepared. Dihydro beta erythroidine is approximately six times more potent than erythroidine. These compounds are absorbed from the gastrointestinal tract more readily than the quaternay bases. They, therefore, are effective if used orally. They are less potent and of briefer dura-tion of action than d-tubocurarine. They cause a nondepolarizing type of block.

PROPERTIES

Beta erythroidine is composed of white needles which melt at 232°C. It has an optical rotation of +109° at 25°C. It is soluble in water, chloroform and benzyl alcohol. It is incompatible with oxidizing agents and alkaloidal reagents. It forms salts with acids, the most important of which is the hydrochloride.

LAUDEXIUM (LAUDOLISSIN)

Attempts at synthesis of compounds similar to tubocurarine lead to the preparation of laudexium. Laudexium (Laudolissin) was synthesized by Taylor and Collier. It is ½ to ¾ as potent as d-tubocurarine; however, it is longer lasting. The structure contains two isoquinoline nuclei whose nitrogens have been quaternized. The quaternary nitrogens are separated the optimal 14 A° distance by a straight ten carbon chain as in the case of decamethonium. Thus, the molecule is a long one like decamethonium and broad like tubocurarine. The compound forms a methyl sulphate which is stable. It is slowly destroyed in the body, the bulk being eliminated unchanged. It is not compatible with alkalis. The duration of action may be one or more hours.

Drug Antagonism and Analeptics

TYPES OF ANTAGONISM

OCCASIONALLY it becomes necessary to antagonize the action of one drug by using another. Antagonism is the reversal, nullification or blocking of the effects of one chemical by another. Three basic mechanisms have been described by which one drug inhibits or overcomes the action of another. These are (1) physiological antagonism, (2) competitive inhibition, and (3) non-competitive inhibition.

PHYSIOLOGICAL ANTAGONISM

Physiological antagonism may be mediated by humoral substances or by pharmacologic opposites. A physiological response is overcome by its natural antagonist or by a substance which acts like its natural antagonist. A segment of arterial smooth muscle, for example, which has been relaxed by the action of acetyl choline, may be made to contract by the action of epinephrine, its physiological antagonist or by ephedrine, its pharmacologic opposite. These substances act at the cholinergic and adrenergic receptors, respectively.

COMPETITIVE INHIBITION

Antagonism by competitive inhibition is brought about when two substances, one of which is physiologically active, and the other physiologically inert, compete for a particular receptor site. The physiologically inactive substance prevents the action of the active one by displacing it from or combining preferentially at the receptor site. The entire response is governed by principles enunciated by the mass action law which are related to reversible combination of substances. The inhibitory effect is, therefore, influenced by the presence of the active substance. One drug may prevent the effects of the other if certain relationships in concentration are maintained. Increasing the concentration of one tends to reverse the effects of the other. Atropine, for example, antagonizes acetyl choline at postganglionic cholinergic receptors. The molecule of atropine becomes attached to the receptor site ordinarily reserved for acetyl choline. A part of the molecule of atropine bears enough similarity to that of acetyl choline so that they both can unite with the same receptor. There is sufficient difference between them so that atropine is inactive. Atropine, therefore, is inert and is devoid of the action of acetyl choline. Therefore, the antagonistic response it causes is produced by preferentially combining with the receptor and thereby preventing acetyl choline from combining and acting at the receptor site. It is a pharmacologic opposite to acetyl choline. Increasing the concentration of acetyl choline displaces atropine from the effector site and reverses the inhibition it has produced.

The union is easily reversible. It is possible, in an isolated biological preparation surrounded by an aqueous environment in which several drugs have immediate access to a receptor site, to titrate one drug against another. However, in the living body such titration is not possible since the drugs do not have immediate access to the receptor sites. Clinicians often refer to the slow intravenous infusion of drugs into the intact animal as titration. The inference in using this term is that a balance is achieved or that a neutralization of one drug by an opposing one occurs. The exact quantitative relationships which are possible in isolated preparations cannot be established in the intact animal because the total quantity of the drug used does not reach a receptor. Some of it is detoxified or stored by other tissues and produces cumulative effects. The portion which does pass to the receptor must run the gauntlet of multiple barriers before it arrives at the locus of action.

Non-Competitive Inhibition

In *non-competitive* inhibition a drug combines at the receptor site to form a stable, less reversible chemical bond. The antagonism is not reversed by increasing the concentration of or removing the opposing drug. In *competitive* inhibition the union is either a physical one or a labile, unstable chemical one which is reversible. The receptor site remains unchanged. In *non-competitive* irreversible inhibition the receptor site is altered. Dibenamine, for example, unites with adrenergic effectors in such a manner that epinephrine and similar acting related amines are unable to displace the drug from this receptor site or act after it has been removed. The nature of the receptor site is altered and re-

mains so for some days after removal of the drug.

ENZYME ACTION AND ANTAGONISM

The effects of certain drugs are intimately concerned with biochemical processes in the cells which are activated by enzymes. Enzymes are protein molecules which possess reactive groups which combine with reacting substances (substrates) to form labile, unstable, intermediate compounds. These labile, unstable compounds, then, decompose forming new compounds plus the original enzyme. Physiological activity may be antagonized by a drug which acts competitively with a substrate for the active groups on the enzyme. Cholinesterase has two active sites, an ionic and an esteractic one. Acetyl choline becomes attached to both of these sites in order to form a labile compound which undergoes hydrolysis to acetic acid and choline. A substance may become attached to one or both of these sites and prevent acetyl choline from reacting with the enzyme. Neostigmine, for example, an antagonist to acetyl choline forms a reversible union at the esteractic site of cholinesterase and thereby prevents the attachment to the receptors necessary for the hydrolysis of acetyl choline. The accumulation of acetyl choline due to failure of hydrolysis produces a sustained parasympathetic effect. Thus, inhibition is competitive because an increase in acetyl choline will reverse the reaction and displace the neostigmine. The inhibition of an enzyme may be non-competitive. In other words, a substance may form a stable, difficult to reverse or even irreversible compound with the enzyme. Its usefulness is thereby destroyed. Alkyl phosphoric acid esters, such as diisopropyl fluorophosphate, for example,

form stable irreversible unions at the esteractic site of cholinesterase. Thus, the acetyl choline accumulates, since it is unable to unite at the esteractic site, and its effect at the receptor site is sustained.

The union of a drug with an enzyme may occur at some site other than the active group. This interaction changes the configuration of the molecule and the enzyme is inactivated. In fact, it may even be denatured since enzymes are proteins. A drug may antagonize enzyme activity by combining with a substrate-enzyme complex. It may also inhibit by preventing the breakdown of such a complex once it forms. In either case the enzyme is removed from the sphere of action. Such inhibition is called *uncompetitive* inhibition to distinguish it from non-competitive. In contradistinction to competitive inhibition the mass action law does not operate in non-competitive and uncompetitive inhibition.

Drugs may increase enzyme activity by acting as a coenzyme or they exert their effect by acting as a substrate in a particular enzyme system. Succinic acid, for example, restores to normal the oxygen consumption of brain slices whose ability to oxidize glucose has been suppressed by barbiturates by acting as a substrate in another energy producing enzyme system which is not poisoned by barbiturates.

ANALEPTICS

Most drugs which antagonize central depression are excitants in the nervous system. Central excitants used to antagonize depression of the nervous system are referred to as *analeptics*. The word analeptic, which is of Greek origin, means *restorative*. The term is, at times, incorrectly applied to cardiovascular stimulants, anti-narcotics, and vasopressors. The term is reserved exclusively for *central stimulants which are used to overcome drug induced depression of the nervous system. Not all central excitants are suitable as analeptics.* Various types may be delineated according to their principal locus of action and their margin of safety. Some act diffusely on the entire neuraxis, others manifest an *initial selective action on some group of* neurons in a localized portion of the nervous system. Some act principally on the cortex, some on the psychomotor areas, some on the respiratory center and other medullary centers. Because of this diversity of action central excitants are classed, in a pharmacological sense, into (1) *spinal cord stimulants,* (2) *medullary* stimulants and (3) *cortical stimulants.* Generally those which exert a primary action on the respiratory center are the most suitable as analeptics. An increase in dosage of most stimulants causes a neighborhood response, that is, the central excitation spreads to other areas of the nervous system. The response may be so intense that it causes convulsions. *As a rule substances which stimulate a structure depresses if used to excess. An excess of most analeptics causes depression, as a rule. Many stimulants have a narrow safety margin.* Of the many substances capable of producing central excitation, few act selectively at the medullary areas and in such a manner that they are useful clinically.

RELATIONSHIP OF CHEMICAL STRUCTURE AND PHARMACOLOGIC ACTIVITY

It is difficult to group analeptics on the basis of chemical structure-physiological activity relationships. The similarities which are so apparent and appear with regular frequency in the congeners

TABLE I.24

R—N   C—R₁   R—N   C—NH₂

Inactive   Stimulant

R—N   C—CH₂—NH₂

Less Stimulating

R—N   C

Depressant

NH₂   N   C—R₁

More Depressant
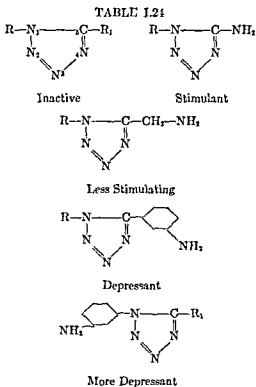
of groups of substances possessing hypnotic activity is lacking in the excitants. Not only is there no similarity between each of the individual drugs in the chemical groups from which the various excitants are derived but there is also little similarity of response between each of the congeners of a series. For example, a series of tetrazoles has been prepared. Of these, metrazol is the only one manifesting well defined analeptic activity. The others are ineffective or may even act as depressants (Table I.24). The clinically suitable compounds, therefore, fall into extremely diverse chemical groups. There is no consistently appearing chemical configuration or grouping which characterizes stimulants. Among the chemical types used clinically are the tetrazoles, the diethyl amides of nicotinic and vanillic acids, the xanthines, the ketones, and the amphetamines. The only similarity which may be considered striking is among a group of diethyl

amides of carboxylic acids. The diethyl amide of nicotinic, vanillic, phthalic and crotonylic acids have medullary stimulating effects.

SIMILARITIES OF EXCITANTS AND DEPRESSANTS

Similarities in chemical structure between central excitants and depressants is striking at times. A slight modification in structure may convert a depressant drug into an excitant. The conversion of the second hydroxyl group of codeine to a methoxy group results in a central excitant (thebaine). Barbiturates may be converted to convulsants by modifying their chemical configuration. Interposing a carbon atom between the phenyl group and carbon 5 in phenobarbital, thus, converting the phenyl radical into a benzyl one, confers convulsive activity to the compound. The imides of glutaric acid such as glutethimide (Doriden) and Bemegride (Megimide) are similar in structure. The former is a hypnotic and the latter a stimulant, and, in large doses, a convulsant. Ethers, particularly the unsaturated aliphatic derivatives, such as vinyl ether, possess, in many cases, central excitatory activity. Hexaflurodiethyl ether which has three fluorine atoms on each of the terminal carbon atoms of diethyl ether is a convulsant which has been proposed by Krantz for shock therapy for the treatment of mental illnesses. More will be said about aspect of these drugs under individual agents.

MODE OF ACTION OF ANALEPTICS

Little is known about the mode of action of analeptics. The physiological antagonism which is so well defined in various organic systems under autonomic control is nowhere as clear cut and as well defined in the central nervous sys-

tem. The response obtained in many cases indicates that possibly two separate effects, depression and stimulation, are operating simultaneously but each is acting at a different locus. In other words, the depressant continues to exert its effect at one site while the stimulant acts at another. Stimulants appear to act in a spotty fashion at one or more isolated areas throughout the cerebrospinal axis. A general uniform antagonism in all structures is seldom evident.

The brain cells apparently mutually regulate their own activity and respond in an orderly fashion with reciprocal antagonism and inhibition between neurons. Substances capable of altering the activity of neurons may disrupt this regulatory balancing mechanism and orderly functioning of neurons and produce disorganization, the end result of which is either anesthesia or excitation followed by convulsions. Since so little is known about the mechanism of action of analeptics and since no specific chemical group may be identified as being responsible for excitation of neuronal structures by these substances, attempts to explain the mode of action are merely speculative.

EFFECT OF STIMULATION ON ELIMINATION OF DEPRESSANT DRUGS

Analeptics do not, as a rule, influence or accelerate the elimination or destruction of hypnotics. Studies using radioactive sulphur indicate that thiopental is metabolized at the same rate when analeptics are administered as they are without. The blood level which ordinarily causes arousal is not influenced by the use of analeptics. Much of the experimental and clinical data indicate that the presence of a depressant drug is necessary for the analeptic to cause the well defined stimulating effect which is characterized by augmented respiration. Smaller doses are necessary to augment reflex activity in narcotized animals than in non-narcotized. In the non-narcotized animals the first sign of excitation may be a convulsion instead of the gradually increasing medullary stimulation. There are several possible explanations for this behavior. (1) The analeptic may act as a coenzyme and activate cellular metabolism. (2) The hypnotic inhibits the activity of inhibitory neurons so that other neurons are free to respond to chemical stimuli. The failure to accelerate metabolism and to increase excretion of the hypnotic is evidence that the depressant and stimulating drug are both acting simultaneously but at different sites. Perhaps in time more light will be shed on this aspect of neuropharmacology. From the foregoing it is inferred that analeptics are of little or no benefit in depression due to non-chemical agents, such as oxygen lack, cold, electric shock or depression due to large doses of depressants. This has been the general experience clinically.

BALANCED ANESTHESIA

None of the analeptics and antagonists acts by competitive inhibition, except the anti-narcotics. In other words true antagonism is virtually unknown among the central excitants. In recent years the term "balanced anesthesia" has been adopted among clinicians. This is unfortunate because the term, which has neither biochemical or pharmacological connotations, infers that one drug opposes or offsets the action of another. It is suggested that at the conclusion of a surgical procedure an antagonist be administered to reverse the depression. This is, of course, erroneous since none

rotoxinin ($C_{25}H_{16}O_6$). Prolonged boiling of picrotoxin in benzine causes it to dissociate into these two substances. If equimolecular portions of these two substances are boiled in water, picrotoxin will crystallize from the solution. Picrotoxin (M.P. 250°C.) is physiologically *inactive*, but picrotoxinin (M.P. 206°C.) is *extremely poisonous*. Picrotoxinin is believed to have a terpinoid skeleton. It is believed that picrotoxin represents an intermediate stage in phytosterol synthesis. A partial structure has been elucidated by several groups of investigators which suggests that picrotoxinin is derived from a steroid by some sort of biological oxidative process.

Aqueous solutions of picrotoxin reduce Fehling's and ammoniacal silver hydroxide solutions. Picrotoxin is oxidized by potassium permanganate in aqueous solutions. Alkaline solutions and alkaloidal reagents do not form precipitates with picrotoxin as do alkaloids. Picrotoxin decomposes slowly in toxicological specimens. Tests for the drug in tissues and body fluids should be performed immediately after removal from cadavers if the drug is to be identified and estimated quantitatively. The drug is readily absorbed from all routes including the oral.

Properties

The picrotoxin is extracted from the fresh berries with alcohol. The substance is a white, odorless, intensely bitter, lustrous, crystalline powder which melts at 200°C. to a yellow liquid. Its molecular weight is 602.27. One gram dissolves in 344 ml. of water at 20°C. and 15 ml. of boiling water. The drug is soluble in alcohol, ether, amyl alcohol, benzene, chloroform, glacial acetic acid, and caustic alkalies. Aqueous solutions are optically active $[\alpha]_D^{18°C} - 29.3°$. The

drug is used as a 3% solution which is stable. For many years picrotoxin was of little interest because its value as a therapeutic agent was not recognized. Its adoption as an antidote for the treatment of coma due to barbiturates and other hypnotics lead to a revival of interest in its chemistry and pharmacology. The drug is the most potent of the analeptics and manifests a comparatively long lasting effect. A latent phase of 5-15 minutes may precede development of excitatory phenomenon. The action may be sustained from 30-60 minutes.

Metabolism

The exact fate of picrotoxin in the body has not been determined. Data regarding its inactivation, since it is so potent and may be highly toxic, are of clinical importance. Dille and Duff observed that the drug disappears rapidly from the blood of dogs and rabbits. The curve depicting the changes in blood level drops rapidly and levels off to a declining base line after twenty minutes. Two hours after a single injection the drug cannot be detected in blood. Traces of convulsion-producing substances are excreted into the urine for as long as eighteen hours after the adminstration of a single so-called therapeutic dose (3 mgm.). Pharmacological studies indicate that single convulsive doses are inactivated within one and one-half hours. Symptoms suggesting cumulative effects are uncommon. Biological tests are usually employed to detect the drug since suitable chemical tests are lacking. Picrotoxin is included in the U.S.P.

CORIAMYRTIN

Coriamyrtin is obtained from the fruit and stems of *Coriaria Myrtifolia*. The structural formula has not been estab-

lished. The emperic formula, $C_{15}H_{18}O_5$, is known. The drug is a solid which melts at 228–230°C. The drug produces convulsions in large doses. Its action, like that of picrotoxin, is medullary.

NIKETHAMIDE (CORAMINE)

Nikethamide is derived from nicotinic acid. The proprietary name Coramine (Ciba) is only one of a dozen less known names. Three carboxylic acids of pyridine are possible, α, β, γ. Nikethamide is derived from the beta acid. The β-carboxylic acid is important physiologically since it is the well known vitamin, nicotinic acid. The acid readily forms the amide. Both hydrogen atoms of the amide are replaceable by aliphatic radicals. The dipropyl, diamyl, diallyl and similar derivatives have been investigated, but the most useful from an analeptic standpoint is the diethylamide, or nikethamide (Table II.24):

TABLE II.24

Nicotinic Acid   Nicotinamide
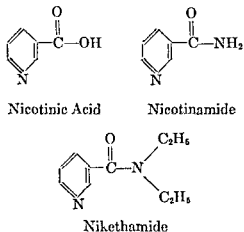
Nikethamide

The central excitatory effect of nikethamide is mostly medullary. Some stimulation of the carotid body has been attributed to the drug but the evidence that it does so is not convincing. The drug possesses a low degree of toxicity. Large doses are necessary to produce frank convulsions.

Preparation

The drug is prepared by interacting thionyl chloride with nicotinic acid and treating the resulting acid chloride with diethyl amine hydrochloride. It may also be prepared by heating nicotinic acid with diethylamine.

Properties

Nikethamide is a yellowish, odorless, somewhat viscous liquid which boils at 280°C. with decomposition. The compound has a faintly bitter taste which is followed by a sensation of warmth. The density of the liquid at 25° is 1.058–1.066. The compound may solidify at room temperature and melt at 24 — 26°. Aqueous solutions have a pH ranging from 6–6.5. The drug is very soluble in water, ether, chloroform, acetone and alcohol. It is usually dispensed for clinical purposes, in the form of 25% aqueous solutions. It is incompatible with sodium carbonate which causes it to precipitate.

Nikethamide is rapidly inactivated in the body. One-half of an injected convulsive dose is inactivated in one and one-half hours. The drug relieves symptoms of deficiency of nicotinic acid. The drug is converted to nicotinamide which is in turn converted to N-methyl nicotinamide. No relationship between nikethamide and nicotinicamide nucleotide has been established. The latter is an important group in coenzyme I and II (Chap. 27).

NEOSPIRAN

Neospiran is the diethyl amide of phthalic acid (Table III.24). The structure of phthalic acid is a benzine ring with two carboxyl groups, one in the 1 position and the other in the 2 position. Neospiran is a solid compound which melts at 39°C. and boils at 175–180°C.

TABLE III.24
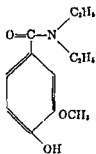
Vandid
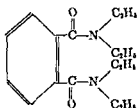
Neospiran
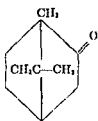
Camphor
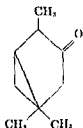
Thujone
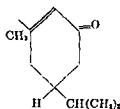
Hexeton
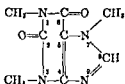
Caffeine
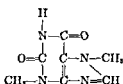
Theobromine
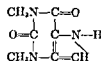
Theophylline

It is quite soluble in water. It is prepared by heating sodium phthalate with diethyl amine phosphate. It is a medullary stimulant similar to nikethamide in pharmacological behavior.

VANDID (EMIVAN)

Vandid is vanillic diethyl amide (Table III.24). The compound is a white crystalline powder which is very slightly soluble in water. It melts at 95.5°C. It acts primarily on the medullary centers.

MICOREN (PRETHCAMID)

Micoren (Prethcamid) consists of a mixture of equal parts of crotonoyl alpha n-propylamino butyric acid diethylamide and crotonoyl α ethylamino butyric acid diethylamide. It differs from the other analeptics in that the amides

are derived from the simple aliphatic acids instead of cyclic derivatives. As is the case with other amides, it is a medullary stimulant and in large doses causes convulsions.

LOBELIA, LOBELINE AND RELATED ALKALOIDS

Source

Indian tobacco, often called wild tobacco, yields several alkaloids called Lobelia. The herb, *Lobelia inflata*, is found in North America, particularly in Canada and the United States. The leaves and tops of the plant are dried, from which numbers of alkaloids are extracted. Of these two are most important —*lobeline* and *lobelidine*. Both alkaloids are isomers. Lobelidine is optically in-

active (racemic form). Lobeline is levorotatory. The compound called *lobeline* is levo-lobeline. Both alkaloids are derived from N-methyl piperidine. Two side chains are placed in the 1 and 5 position.

ganglia. Large doses also depress the heart and exert a curareform action on skeletal muscle.
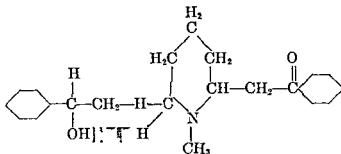
The alcoholic group on the side chain may be converted to a ketonic group to form another alkaloid, *lobelanine*. The latter compound occurs naturally. The ketonic group of lobeline may be reduced so that each side chain now bears a hydroxyl group to form lobelanidine. This is also found naturally.

Properties

Lobeline forms a hydrochloride which melts at 180°C. One gram dissolves in 40 cc. of water or 12 ml. of alcohol. The optical rotation is $\alpha_D^{20} - 42.5$. A commercial product, *lobeline sulphate*, is a mixture of all the alkaloids normally present in Lobelia. *Lobeton* is synthetic lobeline. The free bases of the alkaloids of Lobelia are far less soluble in water than the salts.

Lobeline exerts its effects by stimulating the chemoreceptors in the carotid body. The usual response obtained is several deep gasps which are then followed by inactivity. The action of the drug is transient and variable. Nicotine exerts a similar but less pronounced effect. Lobeline in large doses first stimulates and then paralyzes the autonomic

CAMPHOR

Source

Camphor is a central excitant which acts primarily on the cortex. However, as the dose is increased the brain stem is also stimulated. Camphor occurs naturally but may be also prepared synthetically. Camphor is a *cyclic ketone* derived from the cyclic hydrocarbon, *camphane*. Camphor is the 2-ketone of camphane (Table III.24).

Japan, or naturally-occurring, camphor is *dextrorotatory*. Synthetic camphor may be prepared from the terpene *pinene* (turpentine). The synthetic product is racemic and optically inactive. The chemical properties of camphor are similar to those of other ketones. Camphor forms *oximes* with hydroxylamine. It also may be reduced to the secondary alcohol, *borneol*. Direct bromination yields *brom-camphor*, a derivative formerly used in medicine.

Properties

Camphor occurs as a white, translucent mass, slightly soluble in water, but freely soluble in alcohol and other organic solvents. It melts at 174° to 177°C., volatilizes at ordinary temperature, and

sublimes readily. One part is soluble in 800 parts of water, 1 part of alcohol and ½ part of chloroform. There is no relationship between the structure of metrazol and that of camphor, since the former is a tetrazol, and the latter a ketone derived from camphane.

Metabolism

Camphor is detoxified by conjugation with glucuronic acid by the liver. The byproduct passes into the urine. Camphor is an inefficient respiratory stimulant. Part of this is due to poor absorption. To obviate this objection, more soluble but similar acting substances have been sought. One of these is 3-isopropyl-5-methylcyclohexenone (Table III.24). This is related to camphor and is called *hexeton* or *homocamfin*. The aqueous solubility of this substance is poor also but can be increased by preparing the solution in sodium sulphate or sodium benzoate solutions.

Thujone

Thujone which is chemically allied to camphor (Table III.24) is also a respiratory stimulant. It is obtained from essential oils, particularly thuja. It acts as a central excitant producing convulsions of cerebral origin. Thujone is a colorless liquid. Two isomers are known, the alpha and beta. The alpha is levorotatory; the beta dextro. The compound is a ketone, as is camphor.

CAFFEINE AND RELATED PURINES

Source

Caffeine is an alkaloid, related to purine. Purine occurs widely distributed in nature. The nucleoproteins of most cells contain considerable quantities of *amino* purines. The two chief amino purines, adenine and guanine, are changed in the animal body by various enzymes to the

oxypurines, or xanthines, and finally to uric acid and allantoin. The latter pass into the urine.

Chemistry

The rudimentary structure of purine consists of two molecules of urea in a heterocyclic ring structure of mesoxylal. This structure permits substituents of various radicals on positions in the ring numbered 1 to 9. One oxygen on position number 6 results in hypoxanthine; oxygens in 2 and 6 result in xanthine; while oxygen groups in the 2,6,8 position give trioxy-purine or uric acid.

If methyl groups are placed on the xanthine molecule, three methylated xanthines form—*caffeine*, theophylline, and theobromine. The 1, 3, dimethyl xanthine is theophylline. The 3, 7, dimethyl xanthine, which is prepared from cocao, is theobromine.

Caffeine is the 1, 3, 7, trimethyl xanthine (Table III.24). Caffeine is found in tea and coffee.

Properties

All three drugs are classed as alkaloids. They possess feeble basic properties. The free base of caffeine occurs as white, silky needles. It is odorless and bitter. One part is soluble in 46 parts of water. Aqueous solutions are neutral to litmus. The free base forms salts with organic and mineral acids. The citrate and a mixture of caffeine and sodium benzoate are the most commonly used preparations. The citrate is really a mixture which causes the caffeine to precipitate. Aqueous solutions of the citrate are acid to litmus. The salts are more soluble in water and boilable and stable than the free base. The mixture of caffeine and sodium benzoate contains 50% caffeine by weight.

The purine alkaloids are feeble medullary stimulants. They act primarily on the cerebral cortex. Large doses stimulate the medulla. Convulsions occur only after massive doses.

Metabolism

Caffeine is readily absorbed from all sites including the intestinal tract. A small fraction of a single dose is eliminated unchanged in the urine, but most of the drug is destroyed in the body. Eighty per cent is converted to urea. The eliminated portion consists of di- and monomethyl xanthines. There is no increase or change of uric acid concentration in blood after injection of caffeine.

Caffeine base, caffeine citrate, and caffeine sodium benzoate are the usual available preparations.

AMPHETAMINES

A number of sympathomimetic compounds manifest a central stimulating action in addition to the usual peripheral vasopressor action. Among these are the amphetamines, particularly the dextro, the racemic amphetamine, and methamphetamine (Chap. 22). Ephedrine, likewise, shows some stimulating action, since this is in the amphetamine class. These are little used for analepsis.

METHYLPHENIDATE (RITALIN)

Methylphenidil acetate (methylphenidate, Ritalin) is a central excitant used primarily for elevation of the mood and as a psychomotor stimulant. Large doses increase the activity of the nervous system and produce convulsions. Lethal doses kill by producing convulsions and respiratory arrest. The compound may be considered to be the methyl ester of acetic acid which has one of its hydrogen atoms replaced by a phenyl group and the other by a piperidyl group. The piperidyl group, attached at the 2 position of the nitrogen atom is considered to be in the 1 position (Table IV.24).

The compound is a base which is insoluble in water, but soluble in alcohol, ethyl acetate and ether. A hydrochloride forms which is soluble in water and which is used as a 5% solution. The aqueous solution of the salt is neutral to litmus.

BEMEGRIDE

Structure Activity Relations

Marshall and Vallance studied a series of derivatives prepared by substituting alkyl and aryl radicals on the alpha and beta carbons of the imide of glutaric acid. They were in search of compounds with anti-convulsant properties. They noted that substitution on the alpha carbon atom produced a number of active hypnotics and anti-convulsants. Among these were alpha methyl and phenyl N-methyl glutarimides. The alpha phenyl methyl glutarimide is used clinically as a hypnotic (glutethimide, Doriden). Its action as a hypnotic is similar in behavior to the barbiturates. Substitution at the beta carbon, however, yields compounds which lack hypnotic activity and are inactive or which show central stimulating properties. The beta phenyl and the beta dimethyl glutarimides are inactive. The beta methyl ethyl glutarimide (NP-13, Bemegride, Nikedimide, Eukraton) produce convulsions in large doses (Table IV.24).

Properties

Bemegride is a white, colorless, odorless compound with a slightly bitter taste. It crystallizes from aqueous solutions in regular hexagonal plates. The compound is poorly soluble in water—to the extent of about 7 mgm. per milliliter. It is

TABLE IV.24
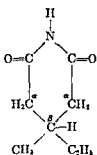
Bemegride, Megimide
(β Methyl, β Ethyl Glutarimide)
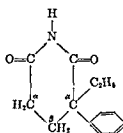
Glutethimide, Doriden
(α Ethyl, α Phenyl Glutarimide)
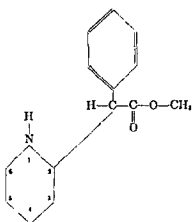
Methyl Phenidate, Ritalen
(Methyl Ester of α Phenyl 2,
Piperidine Acetic Acid)
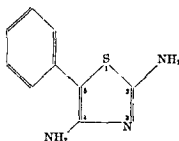
Amiphenazole, Daptazole
(2,4, Diamino 5 Phenyl
Thiazole)

readily soluble in alkalies, in alcohol, ether acetone, chloroform and benzine. Bemegride melts at 127°C. and sublimes under a reduced pressure of 2 mm. Hg to form rosettes or platelets. Aqueous solutions are neutral in reaction. The drug is soluble in normal saline. It is stable to autoclaving at 115°C. for thirty minutes. Bemegride is dispensed in sealed ampules as a solution containing 50 mgm. per ml. The drug is stable. Solutions in normal saline are liable to crystallize if stored in a cool place, since the drug is almost a saturated solution. The ultraviolet absorption of bemegride in ammoniacal solution shows a maximum ultraviolet absorption at 230 mμ.

Metabolism

The exact fate of bemegride in the body is not known. A hydroxy derivative with the oxygen entering the ethyl group in the carbon attached to the beta carbon is found in the urine. This derivative melts at 99°C. and gives a positive reaction with iodoform. The ultra-violet absorption curve of this compound corresponds with that of bemegride (Megimide).

AMINOPHENAZOLE (DAPTAZOLE)

Totally unallied to any of the previously mentioned compounds is a phenylthiazole derivative known by the generic name of amiphenazole (DAPT, Daptazole, Phenamzole, Phenamizole) (Table IV.24). The compound is 2, 4 diamino 5 phenyl diazole. It is prepared by reacting thiourea with alpha cyanobenzyl benzene sulphonide in acetone.

The substance is a base which forms salts among which are the hydrobromide, hydrochloride, the picrate and the benzenesulphonate. This is usually prepared in the form of a hydrobromide or hydrochloride. The base forms flakes from water or dilute alcohol which turns brown on standing in air. The hydrobromide forms prisms from water which decompose at 250°C. The salts are freely soluble in hot water and moderately so in cold. Daptazole is a weak barbiturate *antagonist and believed to be a synergist* to bemegride. The British have used it extensively with bemegride because they feel that it reduces the possibility of convulsions.

SODIUM SUCCINATE

Properties

Sodium succinate is a disodium salt, since succinic acid has two carboxyl groups. It forms a hexahydrate which loses it water at 120°C. The anhydrous salt is soluble in 5 parts of water and insoluble in alcohol. The aqueous solution is neutral or slightly alkaline. A 30% *aqueous solution is used intravenously* as an analeptic.

Mode of Action

Quastel and Wheatly observed that barbiturates inhibit the utilization of glucose, lactate acid pyruvate but not of succinate by brain tissue in vitro. Taubenhaus and Soskin reported that sodium succinate was an effective antidote against pentobarbital in rats. This observation initiated a series of studies by other workers in both animals and man. Other dicarboxylic acids were also studied, such as fumaric and malonic acids. Numerous reports of clinical use of these acids, and, particularly of sodium succinate in barbiturate coma, describe disappointing results. In vitro, however, sodium succinate prevents the depression of oxygen consumption induced by pentobarbital.

The beneficial results which have been reported by some workers could possibly be ascribed to the diuretic effect induced by the large quantities of salt generally employed. Others feel that the drug does not have ready access to the neurons when injected because it is metabolized or diverted to other cells.

PHYSICAL STIMULATION

Physical stimulation has been used in one form or another to attempt to cause arousal. Heat, cold, electricity, pain and pressure have all been tried at one time or another with obviously poor results. Among these methods electrical stimulation deserves some consideration since it is a relatively new method.

ELECTRICAL STIMULATION

Non-convulsive electrical stimulation using the Rieter apparatus has been advocated for the treatment of barbiturate coma. A unidirectional pulsatile current ranging up to 20 millivolts intensity with a frequency of 30–40 cycles per second is directed into the skull through 1″ circular electrodes placed in the temporal regions on the skin. A ripple with a frequency of 100 cycles per second is superimposed on the pulses. Careful study of this technique reveals that augmentation of respiratory minute volume depends upon activation of the peripheral nerves. Wakening time is not shortened nor is protection afforded against lethal doses of barbiturates by this technique. Any apparent beneficial effects which are obtained are due to stimulation of the sensory nerves peripherally. The blood levels remain unchanged.

Standards of Purity of Drugs

SOURCES OF IMPURITIES

THE NEED for absolutely pure anesthetic drugs, is recognized and apparent to everyone. Impurities in drugs may be divided into three classes: (1) those which are formed or introduced *during the manufacture* of the product; (2) those which result from deterioration of the drug *during storage;* and (3) those which result from contamination or deterioration *after breaking the seal.*

IMPURITIES FROM MANUFACTURE

Formation of impurities during manufacture of a drug may be unavoidable. Reliable manufacturers employ the purest reagents and raw materials in processing their wares. Raw materials of an inferior grade or impure reagents may favor side reactions which result in the formation of impure substances. Unavoidable minor side reactions may parallel the main reaction during the manufacture of a drug even though the purest of reagents are used and the utmost care is exercised to prevent their occurrence. Oxidation, reduction, hydrolysis and other side reactions cannot always be avoided. In cases where undesirable substances do form, after all precautions have been taken, such substances must be removed by appropriate methods of purification after the synthesis is complete. Accidental contamination during packing may include substances which

favor deterioration during storage. Thus, clinicians can rely only upon the integrity, honesty, and conscientiousness of the manufacturers and their willingness to conform to regulations imposed by governmental agencies for assurances of purity.

IMPURITIES DEVELOPING DURING STORAGE

Deterioration during storage may be caused or accelerated by the action of physical agents, such as light, heat, and cold. Chemical changes caused by such processes as oxidation, reduction, hydrolysis, polymerizations and tautomerism may be responsible for impurities. Manufacturers pack drugs in containers which exclude light and air to insure the stability of drugs. Preservatives and stabilizers are often added to inhibit the formation of noxious substances, and to prevent deterioration during long periods of storage. Protection of ether from oxidation by contact with metallic copper, the alkalizing of divinyl ether with organic amines and the addition of bisulphite to epinephrine as a stabilizer are examples of such methods of preservation. The addition of bacteriostatic agents or heat sterilization is often necessary to prevent changes caused by bacteria, molds and fungi. In cases where deterioration is unavoidable and difficult to control, even under ideal conditions,

the package is dated and the purity of the drug is not assured by the manufacturer beyond the expiration date. Vinyl ether, for example, is a dated product.

IMPURITIES AFTER BREAKING THE SEAL

One of the commonest sources of difficulties concerning impurities results from the contamination of pure drugs by thoughtless consumers. Drugs may be transferred from the container to unclean receptacles. Drugs affected by light are left in transparent containers. Unstable substances may be inadvertently boiled and heated. Many barbiturates, for example, are unstable if heated. Aqueous solutions deteriorate if allowed to stand. Easily oxidizable or hydroscopic drugs may be exposed unnecessarily to air. Soda lime causes deterioration of certain halogenated compounds. Trichlorethylene, for example, breaks down in the presence of alkali. Tribromethanol, for example, may be affected by highly alkaline water. Tap water may be used instead of the distilled product to form aqueous solutions. Some physicians are indifferent to the expiration date and use drugs beyond dates on the package.

STANDARDS OF PURITY

Medical and pharmaceutical societies have taken the initiative and formulated standards for the purity and composition of drugs. Three publications are available which list data on drugs accepted for clinical use in the United States to which the physician may refer. These are the Pharmacopoeia, the National Formulary, and New and Nonofficial Remedies.* Drugs listed in the Pharmacopoeia are referred to as *official*. However, this does not indicate that the standards formulated in the publica-

* Now known as New and Non-official Drugs.

tion are under supervision of the Federal Government. Drugs, in all three compendiums, are referred to by their generic name and not the proprietary. Thus, Pontacaine which is a proprietary name is described under the listing of tetracaine. The latter is its generic name.

THE UNITED STATES PHARMACOPOEIA (U.S.P.)

The United States Pharmacopoeia lists recognized uses, doses, standards of purity, data on stability, strength of preparations and the nomenclature for drugs and medicinal chemicals used in therapeutics in the United States and its possessions. *In it are also included tests* for identity, quality, and purity of these substances. The *Pharmacopoeia* provides the basis for uniformity of physical and chemical properties of drugs. Substances labeled "U.S.P." must meet the requirements of the *Pharmacopoeia*. Standards are formulated by members of the United States Pharmacopoeial Convention which meets every five years (formerly ten). At this time, preparations are added or deleted from the *Pharmacopoeia* according to their general usage by the medical profession. A supplement is published during the interim if new important drugs warrant inclusion. The Pharmacopoeial Convention is a private body composed of representatives of medical and pharmacy schools, chemical societies and other *scientific* groups. Other countries besides the United States also have established pharmacopoeias.

THE NATIONAL FORMULARY (N.F.)

Important drugs used in a limited extent, which are not included in the Pharmacopoeia, are listed in the *National Formulary* (N.F.). The standards

included in this publication are formulated by a committee appointed by the Council of the American Pharmaceutical Association. The scope of the *National Formulary* is similar to that of the *Pharmacopoeia*. The two organizations work together in comprising standards. Revisions also are made every five years. Drugs which are included in the U.S.P. which are supplanted by other drugs but are still used and are not discarded entirely are included in the N.F. Such drugs likewise are considered official.

NEW AND NONOFFICIAL REMEDIES (N.N.R.)

The Council on Pharmacy and Chemistry was established in 1905 by the American Medical Association to provide authoritative and unbiased information on drugs. Its annual official publication, *New and Nonofficial Remedies*, includes acceptable drugs which are not listed in the U.S.P. or N.F. Standards of purity, uses, dosages, hazards and tests are compiled and published by this organization. Drugs acceptable by and included in this publication are labeled "N.N.R."*

Each organization outlines standards of purity, methods of identification and tests for purity in its publication. Although many of the described tests are simple from the chemist's point of view, they are elaborate or too time-consuming from the clinician's standpoint. Interpretation of tests is often in the realm of a skilled analytical chemist. The clinician should, however, be aware of the standards required.

FEDERAL REGULATORY AGENCIES

Federal regulatory agencies enforce statutes pertaining to drugs. The *Food*

* Now labeled N N D.

and Drug Administration is part of the Department of Health, Education and Welfare. It is charged with the enforcement of the Federal Food, Drug and Cosmetic Act which is designed to regulate the labeling of drugs products. The Public Health Service, also part of the Department of Health, Education and Welfare, exercises control over biologic products. The *Division of Biologics Control* of the National Institutes of Health licenses establishments producing vaccines, serum and other biologic products. The *Federal Trade Commission* has control over advertisement pertaining to foods, drugs and cosmetics. It has the power to prevent the dissemination of false information and misleading advertisements of drugs to the general public. The *Bureau of Narcotics* of the United States Treasury Department administers the *Harrison Narcotic Act* which is part of the Internal Revenue Code. The Harrison Narcotic Act is a *tax measure* by virtue of which rigid controls are exercised over the transportation and distribution of narcotic drugs. The *Post Office Department* indirectly exercises control over drugs by enforcing the *Fraud Section* of the law pertaining to the Fraudulent use of the mails.

Under authority of the Federal Drug and Cosmetic Act the United States Pharmacopoeia and the National Formulary are official compendiums for the products they list and describe. Drugs must meet the standards set forth in these publications. New drugs cannot be released for sale or prescription by physicians without authorization of the Food and Drug Administration. Chemical, pharmacological and clinical investigational data must be submitted to this agency before a new drug is released for use.

ASSAY OF DRUGS

Single tests which are specific and promptly identify a certain chemical substance without further analysis are few. Usually one must perform a series of tests when identifying chemical substances and draw conclusions regarding their nature by deduction. Tests for drugs may be grouped into three classes —physical, chemical and biological. It may be necessary to perform one or several of each type of test before a compound is identified.

Physical Methods of Assay

DETERMINATION OF BOILING POINT

The *boiling point* helps identify a liquid and establish its purity. This is determined by the macro or micro technique. In the former the method of simple distillation is used. The micro method embodies the well known technique of using a capillary tube inverted in another tube of somewhat larger diameter containing the liquid. The vapor in the smaller tube bubbles through the liquid in the larger tube at the boiling point (Fig. 1.25). One may refer to standard texts on organic chemistry or to the *Pharmacopoeia* for the exact technique of both determinations. The boiling point of a pure compound does not vary if the atmospheric pressure is constant. However, if an impurity is present, or another liquid is mixed with it, the boiling point is lowered.

DETERMINATION OF MELTING POINT

The *melting point* is an index of purity of solids. The melting point of a mixture of two dissimilar compounds each having different melting points is lower than that of the higher melting compound. The melting point of a substance is easily

FIG. 1.25. Micro determination of boiling point. Capillary tube sealed at one end is immersed with open end downward into a drop of the liquid. At boiling point of the liquid, bubbles of vapor escape from the immersed end.

determined by shaking one or two crystals of the substance into the bottom of a thin walled capillary tube which is sealed at one end. The tube is placed next to the bulb of a thermometer (Fig. 2.25) and both are immersed in a bath of sulphuric or phosphoric acid. The temperature of the bath is gradually raised until the crystals melt. Melting points of pure substances are sharp. The substance becomes fluid abruptly. Mixtures melt gradually as the critical point is reached.

DETERMINATION OF SOLIDIFICATION POINT

The *solidification point* is an index of purity and helps identify oils, waxes, and fats which are fluid or semisolid at ordinary temperatures. Determination of so-
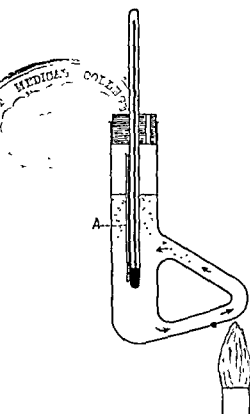
Fic. 2.25 Apparatus for determination
of melting point.

lidification point is equivalent to the determination of melting point.

DETERMINATION OF NON-VOLATILE RESIDUES

Pure liquids evaporate to dryness without residues. The presence of a residue indicates that the substance is impure. Some drugs have an allowable per cent of residues. The quantitative estimation of a residue is easily carried out. A measured amount of a liquid is evaporated to dryness in a clean, flat dish over warm water or in an oil bath or in a current of filtered air. Residues are either non-volatile liquids or solids. Frequently, the impurity may possesses an odor not easily detected in the drug but apparent in the residue after evaporation.

TURBIDIMETRY

Suspension of liquid or solid particles in a liquid causes turbidity. The determination of the *degree of turbidity* in a liquid is frequently an index of purity and a criterion for identification. Suspended solid particles and insoluble liquids may be separated by *centrifugation*. The amount of sediment may be estimated volumetrically in a graduated tube or gravimetrically by filtration and drying. Certain liquids and solutions remain turbid after centrifugation because the particles cannot be separated. In this case the degree of turbidity may be determined by using an instrument known as a *turbidometer*. This measures the degree of transmission of light through the mixture.

DETERMINATION OF SPECIFIC GRAVITY

The *specific gravity* of a substance is a constant value and is, therefore, an excellent index of purity. The specific gravity is defined as the weight of a given volume of a substance compared with the weight of an equal volume of water at a given temperature. Specific gravity may be determined by a number of methods. The simplest methods measure the buoyant effects of liquids. A hydrometer may be used for this purpose. More accurate determinations may be performed by use of a *Westphal balance*. This measures the change in weight of an object submerged in a liquid. Extremely accurate determinations of the specific gravity of liquids require the use of a *pycnometer*. A pycnometer is a glass vessel whose volume can be precisely controlled. This is filled with the liquid in question and weighed. The weight is then compared with the weight of an equal volume of pure water. Specific

gravity varies with temperature so comparisons must be made under identical conditions.

DETERMINATION OF REFRACTIVE INDEX

The index of refraction is a reliable guide to the purity of a drug. Refraction is due to the bending of rays of light. A ray of light passing, at an angle, from one transparent medium to another denser transparent medium is bent towards the perpendicular at the point of incidence (Chap. 7). If a ray passes from air into water, it is bent towards the perpendicular as it traverses the water. This is due to the fact that light travels at different rates of speed in these media. The speed is greater in the rarer medium. The reverse occurs as light passes from a dense to a rarer medium. The ratio of the velocity of light in air to that in water is known as the *index of refraction* for air and water. The ratio is 4 to 3 for air to water, or an index of 1:33. The index varies for each different substance. The index of refraction may be determined for any transparent substance, whether it be a gas, liquid, or a solid, by an instrument known as a *refractometer*. Several types of refractometers are available. One type, known as the Abbe refractometer, is usually employed for assay of drugs. For further details concerning refractometers the reader is referred to the textbooks of physics and chemistry or to the appendix in the *United States Pharmacopoeia*.

DETERMINATION OF OPTICAL ACTIVITY

Nature of Optical Activity

Light may be plane polarized. The ability of a chemical substance to *rotate plane polarized light* is another physical factor which is often used to identify and establish the purity of a drug. Many

organic compounds rotate plane polarized light to the left or right depending upon the configuration of the molecule. Substances which rotate plane polarized light to the left are known as *levo* compounds. This property is indicated by placing an "l" before the name of the compound. Dextro compounds—those which rotate the plane of light to the right—are designated by a "d". A mixture of equal parts of a dextro and levo compound has no optical activity since the rotation of one neutralizes the rotation of the other. One refers to such as a *racemic* compound. Atropine, for example, contains equal portions of dextro and levo hyoscyamine. The substance is optically inactive and is, therefore, racemic.

The Polarimeter

The angle through which the plane of light is rotated is a fixed value for a given chemical compound. This angle may be measured with an instrument known as a *polarimeter* (Fig. 3.25). The principle involved in the use of this instrument is as follows: Ordinary light rays are vibrations which are propagated in all planes perpendicular to the source of propagation. If such a ray of light passes through a crystal of calcite (natural, transparent calcium carbonate) it divides into two rays vibrating in different planes, each perpendicular to the other. As these rays pass through the crystal, both are bent but one more than the other. One of these, the one bent most, is called the *ordinary ray*; the other is called the *extraordinary ray*. If two triangular pieces of calcite are cemented together with balsam they form a rectangular prism known as a Nicol prism (Fig. 3.25). If both of these rays are passed through a Nicol prism, the ordinary ray,
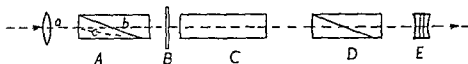
FIG. 3.25. Diagrammatic representation of a polariscope. (A) Nicol prism for polarizing light. (B) Quartz screen. (C) Tube containing solution to be examined. (D) Second Nicol prism. (E) Eye piece. (a) Ray of light entering prism. Ray is broken into two rays, the extraordinary ray (b) which passes on into instrument and ordinary ray (c) which passes to the side and is absorbed by the side of the tube containing the prism.

on emerging from the first half of the prism, is reflected by the balsam cementing the crystals towards the side of the tube holding the prism. It is then absorbed by the wall of the tube. The extraordinary ray is vibrating in one single plane. It, therefore, passes on through both halves of the prism.

Technique of Polarimetry

Optically-active substances may be dissolved and transferred to a transparent container which is placed behind a calcite crystal. As the plane of polarized light passes through the solution, it is rotated at an angle which varies from 1° to 180°, depending upon its molecular configuration. This angle of rotation may be measured by placing a second Nicol prism, behind the solution. This second crystal which is actually an eyepiece can be rotated. As this second prism is rotated, the ray of light, which became visible when the solution was interposed between the two crystals, appears once more. The angle of rotation of the eyepiece is equal to the rotation of the plane of light caused by the chemical. The entire instrument is constructed in the form of a tube.

The angle of rotation is designated by the Greek letter σ (alpha). The source of light must be monochromatic—i. e., it must provide rays of a single wave length. Ordinarily, light emitted by a sodium flame is used. This is obtained by volatili-

zing a sodium compound in a flame. The light from a sodium flame corresponds to the D line of the spectrum. In designating optical activity the wave length of the light used in the determination is noted. The angle of rotation is influenced by the length of the tube, and by the temperature and the concentration of the solution. Therefore, conditions for determining optical activity must be standardized. The linear distance through which the light rays must traverse is usually limited to one decimeter. Distilled water is the solvent of choice. Water insoluble substances, however, are dissolved in alcohol or chloroform. One gram of the substance is dissolved in one cubic centimeter of distilled water. The usual temperature is 25°C. In designating the degree of optical rotation, it is customary to mention the conditions under which the measurement was made $\alpha \frac{25°}{D} = -95°$.

Mutarotation

The degree of rotation of some chemicals varies and changes with the age of the solution. Freshly prepared solutions possess different rotations from those which have been standing for some time. A gradual change occurs until a fixed and constant value is attained. This phenomenon of changing the degree of rotation, known as mutarotation, is explained as follows: In a freshly prepared solution of an optically active substance a

mixture of two optical isomers exists, one of which predominates in amount over the other. After standing for some time some of one type reverts to the other until an equilibrium is established after which the value remains constant.

Asymmetric Carbon Atoms

Optical rotation is due to the presence of an *asymmetric carbon atom* in a molecular structure. An asymmetric carbon atom is one which has all of its valences satisfied by totally dissimilar radicals. A carbon atom having two similar radicals, as, for example, two hydrogen atoms, is not asymmetric and, therefore, possesses no optical activity. *Chloroform* does not possess optical activity because three chlorine atoms are present on one carbon atom. On the other hand, *lactic acid* is optically active because each of the radicals upon the α carbon atom is different. The following formulas of each of the compounds mentioned illustrates this point.

$$
\begin{array}{cc}
\quad\text{Cl} & \quad\text{OH} \\
\mid & \mid \\
\text{H}-\text{C}-\text{Cl} \qquad & \text{CH}_3-\text{C}-\text{H} \\
\mid & \mid \\
\quad\text{Cl} & \quad\text{COOH}
\end{array}
$$
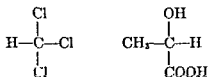
Two asymmetric carbon atoms may be joined together, as in the case of tartaric acid. In this case one may neutralize the optical activity of the other and the compound is optically inactive. In this case the compound is identified by the prefix *meso*. Therefore, four types of compounds with asymmetric carbon atoms are possible—dextro, levo, racemic and meso.

DETERMINATION OF VISCOSITY

Viscosity is also a physical constant which may be used as an index of purity and for identification. Viscosity, which

may be defined as the degree of fluidity, is expressed by a *unit* known as the *poise* (Chap. 2). This unit is too large to express usual values. It is customary, therefore, in chemical studies to speak of a smaller unit or centapoise (1/100 poise). Viscosity is determined by means of an instrument known as a *viscosimeter*. The U.S.P. refers to viscosity in terms of *stokes* (Chap. 2). Viscosity, as is the case with specific gravity and index of refraction, varies with temperature. Therefore, when comparisons are made or values are expressed they should always be at a stated temperature.

Chemical Methods of Assay

GROUPING OF COMPOUNDS

Specific tests which immediately identify a chemical substance are few and far between. Most compounds, therefore, must be subjected to a systemic plan of testing which rules out the presence of or identifies certain groupings and side chains on a molecule and serves to place the compound in a given category. It would be impossible, in a discussion such as this, to go into details and mention anything more than the salient features of this subject. The compound is first identified as being organic or inorganic. If organic the elements other than carbon, hydrogen and oxygen may be identified by fusing the compound with sodium. Nitrogen forms cyanides, sulphur forms sulphides and the halogens form halides by such treatment. The compound is then studied from the standpoint of solubility and reactivity. Its behavior towards oxidation, reduction, hydrolysis, esterfication, halogenation and so on is studied. The presence of specific groups, such as the aldehyde, ketone, amine and so on is determined. This data together with physical properties, such as

boiling point or melting point, appearance, and odor, give clues as to grouping or type.

IMPORTANCE OF SOLUBILITY

Solubility in various solvents provides important clues in regards to grouping. Aldehyde, alcohols and esters are water soluble. Hydrocarbons and compounds related to hydrocarbons are soluble in organic solvents. The degree of alkalinity or acidity also yields important data and should always be determined. The solubility in acids, bases and solutions of electrolytes also yields essential information. Salts are usually more soluble in water than are the organic acids or bases from which they are derived. The barbiturates and the local anesthetics are examples of such behavior.

ALKALOIDAL REAGENTS

Alkaloids and chemically allied synthetic substances form precipitates with certain reagents called alkaloidal reagents, or with alkalies. Alkaloidal reagents are solutions of complex salts of heavy and rare metals, such as gold, silver, tungsten, mercury and so on. These reagents form precipitates with this type of compound which can be identified either by color or crystalline structure. These reagents are described along with the alkaloids in Chapter 16.

CHROMATOGRAPHIC PROCEDURES

Chromatography makes possible the separation and identification of constituents of a mixture that may be present in very small quantities. Extremely small samples may be used—as for example a single drop. The separation is achieved by the aid of two physical phenomenon —*adsorption* and *partition*. Two techniques may be employed—column chromatography and paper chromatography.

In *column* chromatography a glass cylinder is filled with an adsorbent, such as silica gel or aluminum oxide. This is more tedious and used less often. In *paper* chromatography the fibres of a strip of paper serve as the adsorbing agent. Partition involves the distribution of a dissolved substance between two immiscible liquids. One of these liquids is the moisture in the paper; the other is some solvent which is selected which is not miscible with water. In paper chromatography a drop of the solution is placed on a strip of paper and allowed to dry. The strip of paper is suspended vertically in a sealed chamber with one end dipped in a solvent. The solvent traverses the strip by capillary action. When the sample spot is encountered the solvent dissolves the constituents of the spot. A constituent which is extremely soluble in the solvent and has a low adsorptive affinity for the fibres of the cellulose of the paper dissolves quickly and moves along with the solvent. Constituents which have a high adsorptive capacity for the cellulose fibres, a low solubility in the solvent and a high affinity for the moisture in the paper remain in the area. Thus, the constituents in the spot move at different rates depending upon their relative solubility in the selected solvent and moisture and their adsorbability. The spot, therefore, moves down the paper and is separated into isolated spots at different areas on the paper. After separation, the paper with the spot, referred to as a *chromatogram*, is dried. Colorless constituents are made visible by treating with reagents which produce colored products or by viewing under ultra-violet light. If an electric current is passed through the paper the resolving power is increased. This is known as *paper electrophoresis*.

COLORIMETRIC AND PHOTOMETRIC METHODS

As in the case of identification and quantitative determination of gases (Chap. 7) solids dissolved in liquids or liquids dispersed in other liquids absorb radiant energy. This energy may be visible light of different wave lengths which may be quantitatively determined by a *colorimeter* or it may be invisible radiation, such as ultra-violet light or infrared rays. A compound may selectively absorb ultra-violet light of a given wave length. This property serves to identify it as well as to quantitatively determine the concentration present. Thiopental, for example, behaves in this manner and selectively absorbs ultra-violet light of a given wave length.

A device which measures the intensity of a beam of light transmitted through a substance is known as a *photometer*. A spectrometer is a device for producing colored light. When combined with a photometer it is called a *spectrophotometer*. When the combination is used to emit and measure the absorption of light of a single wave length it is called a *monochromometer*. When invisible radiation is used (ultra-violet light) the substance absorbs the energy and limits visible light or fluorescence. The intensity of this emitted visible radiation is measured with a *fluorometer*. Inorganic substances may be identified and measured quantitatively by means of a *flame photometer*. The substance is introduced at a constant rate into a hot flame and the intensity of the light emitted is measured by a spectrophotometer. These devices, therefore, are useful in establishing the identity of chemical compounds and determining whether or not foreign substances are present.

PREPARATION OF DERIVATIVES

After all the physical and chemical data have been collected and assembled, the identity of the substance may be confirmed by preparing a *derivative*. Preparing a derivative consists of converting the substance to another product by some method of synthesis. Ethyl alcohol, for example, may be esterified with acetic acid and converted to its ester, ethyl acetate. This can be identified by its physical properties.

ISOLATION OF IMPURITIES

Reagents and test solutions are usually prepared using water as the solvent. When the drug and the test chemicals are not soluble in water, solvents, such as alcohol, ether, and benzine and so on are used. When the suspected impurity is soluble in water but the drug containing it is not, the specimen may be extracted with water. Thus, when ether is tested for impurities, it is shaken with water in which it is relatively insoluble. Acids, peroxides, and aldehydes which constitute the important impurities, pass into the aqueous layer to which the reagents for their detection are added.

TESTING FOR IONIZABLE SUBSTANCES

Inorganic ions are detected by tests which are, by and large, specific. An aqueous solution of barium chloride yields a heavy white precipitate when added to solutions containing sulphate ions due to the formation of insoluble *barium sulphate*. Silver nitrate in concentrated nitric acid yields white or yellow precipitates when added to solutions containing halide ions. The *chlorides, bromides,* and *iodides* of silver are insoluble in nitric acid. *Phosphates* may be detected by using a magnesium and ammonium chloride reagent to form the in-

soluble magnesium phosphate. *Carbonate* ion and carbonic acid are detected by using saturated barium or calcium hydroxide solutions. A white precipitate of the carbonate forms. The *alkaline earth metals* are detected by the addition of the sulphate ion. Barium, calcium, and strontium sulphates are insoluble and form white precipitates. The *heavy metals*, such as silver, copper, and mercury, are precipitated by bubbling hydrogen sulphide through aqueous solutions containing the ions. The black precipitates which form are the *sulphides* of these metals. Iron, zinc, manganese, and cobalt also produce insoluble sulphides.

Biological Assay

In some cases it is not possible to identify the drug by chemical methods because no specific method is available or because of complexity in structure. Certain such unidentifiable substances possess physiological actions which characterize the drug. These tests are carried out on pieces of living tissues, frogs, and various intact laboratory animals. Such responses as contraction of smooth muscle strips, slowing of the heart rate, raising of the blood pressure, stimulation of respiration and production of convulsions, are used to estimate the amount of active substance in a preparation or to detect the presence of undesired substances. Sometimes it is impossible to determine the quantity in units of weight or volume, such as milligrams or milliliters. The quantity is then expressed in units. A *unit* is the amount required to produce a certain physiological effect under a certain set of standardized conditions. For instance, quantities of pituitrin are expressed in units. A unit is the amount required to raise the blood pressure of a dog to 30% of its control level in a certain number of minutes. The exact amount of the principle in grams in the dry gland is not known. The dose of curare was expressed in units prior to the isolation of the pure alkaloid, tubocurarine. The physiological test known as the *head drop crossover technique* was used for assay in terms of units. One unit of curare is equivalent to the amount of active principal which causes the muscles of a rabbit weighing 1 kg. to become flaccid so that the animal can no longer support the head. Now that tubocurarine has been isolated from curare and is available in pure form the dose is expressed in milligrams of crystalline alkaloid.

Flammability of Anesthetic Gases and Vapors

THE NATURE OF COMBUSTION

CHEMICAL NATURE OF COMBUSTIBLE SUBSTANCES

MOST ANESTHETICS are organic substances and most organic substances are combustible. A substance must combine with oxygen to be combustible. In other words, it must be oxidizable. Most organic substances contain carbon, hydrogen and oxygen. Less frequently, they contain other elements such as sulphur, nitrogen or the halogens. The presence of carbon and hydrogen favor oxidation. One must distinguish between *combustion* and *oxidation*. All oxidations cannot be classed as combustion. The term *combustion* is used to describe the oxidation of organic materials whose end products are carbon dioxide and water. The rusting of iron *is* oxidation but not combustion. The conversion of glucose to carbon dioxide and water *by the cells is oxidation, but not* combustion. The rate of oxidation of a substance varies with its chemical nature and the environmental conditions. In everyday language, substances which undergo rapid, almost instantaneous, oxidation are referred to as *flammable*.

Anesthetists refer to the inadvertent combustion of flammable anesthetics as being either a fire or an explosion. The basic difference *is merely in the rate of* oxidation. In a *fire* oxidation occurs

slowly. An *explosion* is a detonation in which oxidation is almost instaneous and the by-products and energy evolved are dissipated rapidly. These aspects of combustion are discussed further on.

SUBSTANCES WHICH SUPPORT COMBUSTION

A distinction must be made between a combustible substance and one which supports combustion. A substance which supplies the necessary oxygen for combustion *supports* combustion. Nitrous oxide, for example, *supports* combustion because it readily relinquishes its atom of oxygen to a substance already undergoing oxidation. However, it is not combustible because it adds additional oxygen atoms with difficulty.

ENERGY EXCHANGE DURING OXIDATION

Oxidation of most substances, with rare exceptions, is accompanied by the evolution of heat. In other words, the reaction is almost always *exothermic*. A reaction accompanied by the absorption of heat is referred to as an *endothermic* reaction. Instances in which the union with oxygen are endothermic are few. The formation of nitrous oxide from the elements is an endothermic reaction. The rapid evolution of heat during combustion causes luminescence and incandescence of the interacting substances and the evolved gases. A flame results.

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BY-PRODUCTS OF OXIDATION

The by-products of complete oxidation of organic substances composed of carbon, hydrogen and oxygen are water and carbon dioxide. Oxidation of a substance may not always proceed to completion, however, and partly oxidized by-products may form. For example, the incomplete combustion of alcohol may yield aldehydes and acetic acid in varying proportions along with the carbon dioxide and water. The heat output is not as great. The resulting flame may be of low visibility and often not visible except in the dark. Such a flame is referred to as "*cool flame.*" Carbon is the only combustible material which yields only carbon dioxide when completely oxidized.

Molecules containing other elements besides carbon, oxygen and hydrogen yield a multiplicity of by-products when oxidized. Substances containing nitrogen yield a mixture of nitrogen oxides, ammonia and amines in addition to carbon dioxide and water. Compounds containing sulphur may yield sulphates, sulphites and complex mixtures of sulphur oxides besides carbon dioxide and water. The nature of the resulting products of such complex molecules depends upon general conditions, such as temperature, concentration, pressure and amount of available oxygen.

EFFECT OF HALOGENATION UPON FLAMMABILITY

Halogenation of organic compounds decreases their flammability and, in many cases, renders them non-flammable. The greater the number of halogen atoms on a molecule the less the flammability of a compound. For example, methyl chloride (monochlormethane) is flammable; dichlormethane is less so, while trichlor-methane (chloroform) and carbon tetrachloride do not burn. The oxidation of halogenated compounds yields complex halogenated oxides and halo acids form in addition to water and carbon dioxide.

FACTORS INFLUENCING PRODUCTION OF EXPLOSIONS

A combustible substance may be a gas, liquid or a solid. Inhalational anesthetics are either gases or easily volatilized liquids. The rate of oxidation of a flammable substance depends upon the total number of molecules of a gas or vapor, the number of molecules of oxygen, how intimately these molecules are mixed with the reactants, the rapidity with which the released energy is dissipated and the degree of dilution of the reacting agents with the by-products.

A portion of ether in a beaker, for example, burns vigorously over a period of many seconds because only the surface molecules have access to oxygen; the others in the interior of the liquid do not. A fire results. The same number of ether molecules vaporized and intimately mixed with oxygen oxidize instantaneously when ignited. Theoretically, the energy released in each case is the same and the by-products which form are the same, but all this occurs in a far briefer interval of time. If the reaction occurs in a closed space the hot gases expand with violence. A solid oxidizable substance pulverized into a dust and suspended with oxygen undergoes rapid oxidation. A block of wood, if ignited, burns gradually with the liberation of heat, light, water and carbon dioxide. The same block of wood finely pulverized and suspended in air or oxygen explodes when ignited.

Mixtures of flammable anesthetic gases and vapors in semi-closed and

closed inhalers are more apt to explode than cause a fire because they are intimately mixed with oxygen. The incidence of explosions has increased since the adoption and extensive use of closed inhalers. Ignition of flammable materials using open techniques of administration is more apt to cause a fire rather than an explosion.

The primary requisites for an explosion are that a combustible substance be intimately mixed with air or oxygen. However, other factors influence the propagation of flames in such mixtures. Among these are (1) the size, shape, thickness and composition of the vessel containing the flammable mixture. (2) The pressure of the mixture. (3) The temperature of the mixture, of the container and of the environment. (4) The percentage composition of the mixture. (5) The flashpoint of the combustible substance. (6) The ignition temperature. These factors are discussed further on.

TYPES OF EXPLOSIONS

Disintegration of Molecules

Explosions are not all caused by rapid oxidation, however. The molecules of certain substances, such as nitroglycerin, for example, are so unstable that an internal rearrangement of atoms may occur. This reaction is accompanied by the liberation of energy and molecules of gases and vapors. Such a rearrangement of atoms occurs instantaneously. The liberated gases and vapors expand with destructive violence.

Detonators

Organic compounds containing nitrogen, particularly nitrites and nitrates, are unstable and undergo such an internal rearrangement of atoms. Vapors and gases consisting of nitrogen, nitrogen oxides, steam and carbon dioxide are liberated instantaneously. A shock-like external force, such as a lesser explosion from a cap, is required to initiate this disintegration of unstable molecules. Heat, an electric spark or even a mechanical blow may initiate the change. An agent which initiates an explosion is referred to as a *detonator*. The cap used to explode dynamite and the spark which ignites a flammable anesthetic are detonators.

Release of Gases at High Pressure

Explosions may also result from purely physical phenomena in which no chemical reaction is involved. The rupture of cylinders containing compressed gases at high pressures is an example of such a phenomenon. The sudden release of the entrained energy in such containers causes considerable destruction. The majority of explosions associated with anesthesia are due to ignition of combustible vapors and gases.

FLAMES, DEFLAGRATION
AND DETONATIONS

Combustion is associated with the emission of light. The zone of combustion which emits light is referred to as a *flame*. Flames are classed as *static* and *movable* (or *self-propagating*). The flame of a kerosene lamp is static since the vaporized hydrocarbon mixes with oxygen at a given rate, at a particular zone close to the wick. A self-propagating flame is one in which the zone of oxidation advances through the flammable mixture. This advance may be seen if a transparent tube several inches in diameter, open at one end, is filled with a flammable mixture. A source of ignition placed at the open end causes a flame to develop which advances in-

ward and continues to travel the entire length of the tube. This advancing zone of oxidation, referred to as a *front*, is visible to the naked eye. The heat of combustion in the advancing front warms the adjacent layer of combustible mixture and initiates combustion in that layer. The combustion spreads forward in the tube from layer to layer. Such a self-propagating flame is often referred to as a *deflagration*. The reacting substances in the advancing layer are converted to the final products very rapidly—within 0.3 to 0.4 of a millisecond. The temperature of the advancing front is raised to 1500°C. or above. This rapid release of energy increases both the temperature and pressure of the gases. In an open *tube* the gaseous by-products stream backward into the atmosphere in the direction opposite to the propagating flame (Fig. 1.26). This occurs as quickly as the gases expand. No pressure of great magnitude develops. In a *closed tube* the burned gases are unable to rush backward. Instead, they advance forward in the direction of the propagation of the flame. The expanding gases push the flame forward. The flame advances along the tube at a speed which equals the speed of the flame plus the speed of the advancing gases. When the speed of the advancing flame is very rapid, the liberation of heat in each successive forward layer occurs at an increased rate. The temperature in the advancing flame increases progressively. There is insufficient time for equalization of the pressure. The compression of these advancing gases further augments the heating. The temperature rises so rapidly that it exceeds the ignition temperature of the mixture. The rate of reaction, thus, becomes exceptionally rapid. Ultimately, a zone of gases at high pressures develops. This zone expands and sends out a wave which travels at supersonic speeds. This wave of high pressure gas is referred to as a *shock wave* (Fig. 2.26). The liberated gases expand with destructive violence. Such a violent reaction is known as a *detonation*. The propagation of a flame in a deflagration is not rapid. It occurs slowly, comparatively speaking, at rates of several meters per second. The speed of the shock waves in a detonation may exceed 3000 meters per second. Temperatures are far higher than in a deflagration. Temperatures ranging from 3000-3600°C. may develop. Pressures, likewise, are higher. Pressures of 25 or 30 atmospheres are
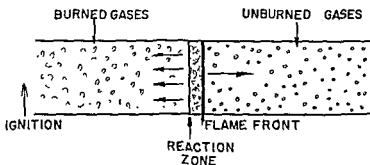
Fig. 1.26. The propagation of a flame in an open tube The gas is ignited at the open end. The burned gases rush backward in the direction of the arrows. The flame front ahead of the reacting zone advances forward into the unburned gases
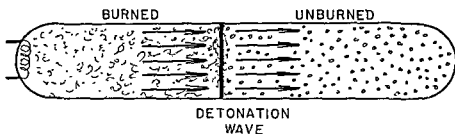
DETONATION
WAVE

Fig. 2.26. In a closed tube the detonation wave moves at a high speed into the unburned gases. The burned gases advance forward in the same direction as the wave instead of backward as in an open tube (Fig. 1.26).

possible if the areas of high pressure remain static. If the gases in an expanding wave encounter an obstruction, the impact of the successive waves following the initial wave augments the pressure and enhances the violence of the detonation.

INITIATION OF OXIDATION

A chemical reaction consists of the interaction of atoms which are drawn together by mutual attraction. Strong forces of attraction result in the formation of stable molecules. This process of forming stable molecules is known as *bonding*. Energy is released when bonding occurs. In other words, the reaction is exothermic. Should a molecule be divided into its component parts the energy which was released when bonding occurred must be restored. The reaction, then, is an endothermic one. After bonding has occurred the resulting similar molecules tend to repel each other and other molecules. Collisions of individual molecules are averted by this repulsion. Collisions would result in interaction of the colliding molecules.

At room temperatures the molecules of a flammable agent, as for example, ether, co-exist with those of oxygen without interacting. They do not interact because they are kept apart by repellent forces as they approach each other. Some molecules in an aggregate move

faster than others. A fast moving (high energy) molecule may overcome the force of repulsion and thereby collide and interact with another. Such collisions are infrequent, because, at room temperature, the high energy molecules are relatively few in number. Oxidation is occurring in a molecular aggregate at room temperature but at an extremely slow rate because of the fewness of fast moving molecules. The process may be accelerated by nullifying the repellent forces between molecules by instituting a state of mutual attraction. This is accomplished by increasing the speed of the molecules reacting so that collisions between the ether and oxygen are more frequent. Energy, therefore, in the form of heat, must be added to the mixture. The proportion of high energy collisions rises rapidly as the temperature rises. As the molecules interact a regrouping and rebonding of atoms occurs with the subsequent formation of new products and a release of energy.

Combustions are exothermic reactions; therefore, energy is released when the ether and oxygen interact. Once a sufficient number of high speed collisions has been provided large quantities of energy known as the *heat of combustion* are released. Thus, energy from an external source known as the *activation energy* must be added to *initiate the reaction*. This activation energy is recouped from

the heat of combustion. The energy released by combustion is many times greater than the original activating energy and acts as the activating energy for the contiguous layers of oxidizable mixture. As the temperature rises the speed of a chemical reaction is increased. Ordinarily it is doubled for each 10°C. rise (Arrhenius' Principle). Thus, the entire mass oxidizes almost instantly because the resulting temperature is of great magnitude.

RANGE OF FLAMMABILITY

Limits of concentrations exist for a particular combustible mixture above which and below which ignition does not occur, regardless of the efforts made to initiate the reaction. All concentrations between these limits ignite. The per cent concentrations between these limits is called the *range of flammability*. The ranges of flammability for most combustible anesthetics have been determined in the laboratory under controlled conditions. The method, the importance and the value of the data obtained are described further on.

The lower limit of flammability of most anesthetic gases and vapors ranges between 1 and 3%. The upper limit varies from 60 to 80% (Table I.26). In all instances, with the exception of trichlorethylene, the anesthetic concentration lies within the range of flammability.

THE INFLUENCE OF CONCENTRATION OF GASES

The weakest mixture through which a flame propagates is called the *lower limit of flammability*. In a mixture of lower concentration the number of molecules of a combustible substance combining with oxygen molecules is too few to heat adjacent layers of mixture to cause propagation of a flame. Thus, even though the number of oxygen molecules is more than adequate, the number of molecules of a flammable substance are too few to cause a reaction of any magnitude. Oxidation occurs in these dilute concentrations but the energy released is insufficient for self-propagation of a flame.

The molecules of a combustible substance may be so numerous that they outnumber those of oxygen so that the number undergoing oxidation is too few to release sufficient energy to propagate a flame. The concentration of flammable mixture above which the number of molecules undergoing oxidation is insufficient to propagate the flame is called the *upper limit of flammability*.

CONCENTRATION OF OXYGEN FOR IGNITION

The minimum concentration of oxygen in a mixture, likewise, is a most important factor. No mixture, no matter what the concentration of combustible

TABLE I 26

Gas	Lower Limit			Upper Limit		
	Air	O₂	N₂O	Air	O₂	N₂O
Ethylene	2 8	2.9	1.9	28	80	40
Propylene	2.0	2 1	—	11	53	—
Acetylene	2.5	—	—	80	—	—
Cyclopropane	2 4	2.4	1.6	10	63	30
Ethyl ether	1.8	2.1	1.5	36	82	24
Divinyl ether	1 7	1 8	1.4	27	85	25
Vinyl ethyl ether	—	—	—	—	—	—
Ethyl chloride	4.0	4.0	21	15	67	33
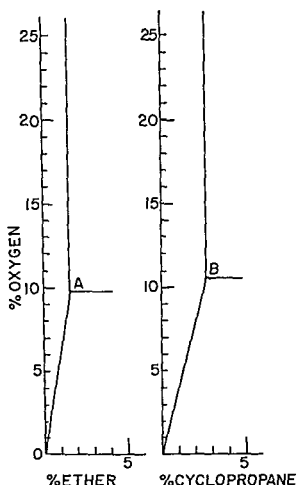
FIG. 3.26. The concentration of oxygen necessary to actively support combustion plotted against concentration of cyclopropane and ether. The minimum oxygen concentration and the minimum of ether intersect at (A), the minimum of cyclopropane and oxygen intersect at (B).

substance may be, forms a self-propagating flame if the concentration of oxygen molecules falls below a certain value. The number of molecules of combustible substances which interact with oxygen are then too few to heat the adjacent layers to cause propagation of the flame. The concentration of oxygen below which self-propagation does not occur is usually less than 10% by volume. Curtailing the flammability of anesthetic mixtures by decreasing the oxygen content is not feasible clinically because the minimal oxygen tension necessary to

support combustion is, in every instance, less than the physiological needs of the patient (Fig. 3.26). Besides, oxygen rich mixtures are necessary and desirable for anesthesia with most drugs. Oxygen rich mixtures with adequate concentrations of combustible substances permit rapid oxidation and set up ideal conditions for rapid propagation of flames and for detonations.

IGNITION OF FLAMMABLE MIXTURES

FLASHPOINT

Flammable gases or vapors mixed with adequate amounts of oxygen do not ignite at extremely low temperatures even when exposed to vigorous sources of ignition. If the particular liquid from which a vapor is derived is gradually warmed a certain temperature is reached at which ignition occurs. However, combustion does not continue unaided when the ignition source is withdrawn. In other words, the vapor ceases to burn when the flame is withdrawn. The temperature at which a vapor first burns is referred to as the *flashpoint*. The flashpoint is the lowest temperature at which enough molecules of a gas or vapor are present to produce an ignitable mixture which results in a flame when an ignition source is passed over the surface of a liquid. The flashpoint of most combustible anesthetics in common use is far below 0°C. The flashpoint of a liquid is not easily determined because many extraneous factors make its precise determination difficult, if not impossible.

IGNITION TEMPERATURE

Flashpoint must not be confused with ignition temperature. *Ignition temperature* is the point at which a flammable mixture ignites and continues to burn unaided when the source of ignition (flame

TABLE II 26
IGNITION TEMPERATURE OF
FLAMMABLE ANESTHETICS

	In Air	In Oxygen
Ethylene	490°C.	485°C.
Cyclopropane	498	454
Ether	359	304
Divinyl Ether	360	327
Ethyl Chloride	502	468

or spark) is withdrawn. The temperature to which a vessel containing a flammable mixture must be heated before deflagration occurs is known as the *spontaneous ignition temperature*. The ignition temperature of most of the common anesthetics is between 300–500°C. (Table II.26). The ignition temperature is not a constant finding for a particular combustible substance. It varies with the type of spark or flame, the composition of the mixture, the pressure of the mixture, the rate of heat loss and other factors.

MODE OF IGNITION

The ignition temperature is less than the resultant temperature of the molecular aggregate undergoing oxidation. In other words, the resulting flame is hotter than the spark which initiates combustion. In a spark or flame ignition occurs in a highly localized area of the molecular aggregate. In a spark a small volume of the flammable mixture is raised to the ignition temperature. Heat is released to contiguous layers surrounding the spark which in turn are elevated to or above the ignition temperature. Thus, a spark or flame of very small volume starts a self-propagating flame through an entire mass of flammable mixture. The propagation continues even after the ignition source has been extinguished or is withdrawn. The rate of heat loss plays an important role in propagation of a flame once the ignition source has been applied. If heat loss

occurs at and is maintained at the same pace as heat production the process is referred to as *isothermal oxidation*. Heat loss may exceed heat production in which case the reaction is interrupted and combustion ceases.

DETERMINATION OF LIMITS OF FLAMMABILITY

TYPE OF APPARATUS USED

The limits of flammability and the ignition temperatures of a particular mixture of gases are not easily determined because a number of variable factors are involved. The results of such determinations vary with conditions of the experiment, such as the time required to initiate combustion, the type of equipment employed to make the test, and the type of ignition source used to initiate combustion and so on. The apparatus devised by Coward and Hartwell (Fig. 4.26) fixes all variables except the composition of the mixture. The apparatus has been used to determine the range of flammability of most anesthetic mixtures. The apparatus consists of a glass tube four or five feet long and approximately 2" in diameter. This diameter appears to eliminate the cooling of the reacting molecules by the wall of the container. Tubes having diameters greater than 2" influence the results little or not at all. Diameters less than 2" cause significant variations in results due to heat loss. Heat loss is greater in narrower tubes. In spheres, likewise, heat loss varies with size. Flame propagation is more difficult to establish in a small sphere than a large one, all other factors being constant. The tube must be of sufficient length to permit the observer to distinguish between propagation and a flash and to determine the rate of propagation. Glass is used for
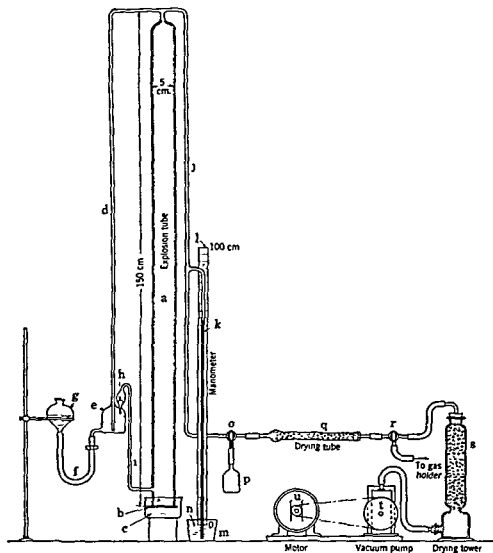
FIG. 4.26. Apparatus used to determine limits of flammability of anesthetic mixtures. The inverted tube (a) is sealed with glass plate (b) which is immersed in pool of mercury (c). The tube is evacuated with pump (t). The gas to be studied is admitted by turning stopcock (r) which is connected to gas holder. The assembly (e,f,g,h) is used to equalize the pressure in the tube with that of the atmosphere and to allow excess gas to escape. The pressure is determined with the manometer (k). Ignition source is applied to mouth of tube by removing (b). *From Anesthesia and Analgesia, 21:121 (June 3) 1942. (Courtesy of Drs. G. J. Thomas and G. W. Jones and Anesthesia and Analgesia.)*

the container because of its transparency and poor heat conductivity which helps to eliminate discrepancies caused by rapid conduction of heat, such as would occur if metals were used. The thermal conductivity of glass is far less than that of most metals. If the concentration of a combustible substance is not within the range of flammability, a cap-like flame develops at the mouth of the tube upon application of an ignition source. The flame is extinguished upon withdrawal of the ignition source. When the concentration falls within the limits of flammability, the cap is propagated the entire length of the tube. The rate depends upon the composition of the mixture. Usually it is 4 or 5 meters per second.

TECHNIQUE OF TESTING

The apparatus is designed so that tests may be performed at atmospheric pressure and room temperature. The combustion tube is sealed at the top and open at the bottom. A stopcock is placed at the top for attachment of a vacuum pump for exhaustion of the tube, so that it may subsequently be filled with the mixture to be tested. The lower end is sealed by placing a plate over the mouth and submerging it in a vessel containing mercury. A thoroughly dried test mixture is introduced into the evacuated tube until the pressure is slightly above that of the atmosphere. The excess gas is then allowed to escape so that the pressure is equalized with that of the atmosphere. The mixture is then ignited by lifting the tube from the mercury pool and removing the gas plate. A hydrogen flame, alcohol lamp, spark or other source of ignition is passed over the mouth of the tube.

The position of the tube is important. If the tube is placed horizontally one set of values is obtained while if it is placed vertically, even though all other conditions are identical, a different set of values is obtained. The day to day variations in atmospheric pressure and in laboratory temperature cause no appreciable discrepancies in the results. The type of flame used as the ignition source, of course, makes considerable difference in the results obtained. Some mixtures are more easily ignited by one type of flame than by another. A mixture of helium, cyclopropane and oxygen is less easily ignited by a spark produced by an electrical discharge than by a naked flame.

It must be emphasized that the ranges of flammability have been obtained in the laboratory under controlled conditions. The per cent composition of a mixture which is flammable under laboratory conditions may respond differently to ignition sources under clinical conditions.

MEASUREMENT OF EXPANSILE FORCE

The pressure of the expansile force developed during detonation of flammable mixtures in a closed space is difficult to measure. A number of techniques have been devised but no one is satisfactory. In one technique the mixture is placed in a bomb of 8 liters capacity and ignited. The resulting pressure is measured. Studies of this sort are not only difficult to undertake but yield results of questionable value because too many variable factors are involved. Jones and Combers found the maximum pressure developed by a mixture of 5.5% cyclopropane and air at 25°C. at 742 mm. Hg pressure to be 98 lbs. per sq. in. above atmospheric. Insurmountable difficulty was encountered in measuring the pressure generated by cyclopropane oxygen rich mixtures because of the extreme violence of the chemical reaction.

THE EFFECT OF NON-OXIDIZABLE GASES OR QUENCHING AGENTS ON FLAMMABILITY

MODE OF ACTION OF QUENCHING AGENTS

Considerable data has accumulated concerning the quenching or damping effects of non-oxidizable inert gases added to flammable mixtures. The presence of nitrogen, helium or carbon dioxide narrows the range of flammability. The lower limit is raised and the upper limit is lowered by the admixture of these agents. The effect obtained is due, to a great extent, to lowering the tem-

perature of the ignition source. In addition, conditions are so altered that a higher ignition temperature is required to initiate oxidation. Mixtures composed of air and a combustible substance have a narrower range of flammability than those composed of pure oxygen and a combustible substance because the nitrogen acts as a quenching agent. The cooling of a spark by inert gases is due to either one of or a combination of two factors. These two factors are the *molal heat capacity* and the *thermal conductivity* of the quenching agent. The heavier the molecule of the gas the greater the molal heat capacity. The molecule of nitrogen is fourteen times heavier and, therefore, possesses a higher heat capacity than that of helium. It should, therefore, be more effective as a quenching agent than helium. However, the quenching effects of the two gases are nearly alike. This is explained by the fact that the thermoconducivity of helium is approximately six times greater than that of nitrogen. This greater conductivity compensates for the low heat capacity and accounts for the equality of the quenching power. Carbon dioxide is effective because of its high heat capacity. However, it cannot be used because concentrations of 5% or more are necessary in an anesthetic mixture to be effective. Such concentrations, obviously, are impractical because deleterious physiologic effects would ensue. The concentrations of carbon dioxide ordinarily inspired have no appreciable quenching effects. Mixtures containing helium are more difficult to ignite by electrical discharges than those containing nitrogen. Therefore, helium possesses some advantage as a quenching agent because the majority of explosions associated with anesthesia are caused by sparks due to static electricity. The lower limits of flammability are not altered by inert gases to the same extent and proportions as are the upper limits (Figs. 5.26; 6.26). The upper limits are reduced to a greater degree.

USE OF HELIUM FOR QUENCHING

Thomas, Jones and their associates, have advocated the use of helium for quenching. A mixture of 15% cyclopropane, 20% oxygen and 65% helium does not ignite. Combinations of 25% cyclopropane, 25% oxygen and 50% helium or 30, 30 and 40, likewise, do not ignite. Such mixtures have been recommended for clinical use. Although, theoretically, the use of such mixtures appears sound, clinically they are impractical. Such mixtures afford protection only during the maintenance phase of anesthesia provided the concentration of gases is not varied. During the induction of anesthesia, when the air in the breathing bags, tubes, cannisters and the patient's lungs is being mixed with the nonflammable mixture, a flammable mixture may form as a result of the dilution. At the termination of anesthesia, as air is admitted into the apparatus and into the lungs dilution occurs and the mixture is brought within the flammable range. Ignition may occur at this time. Even during maintenance of anesthesia one is not assured of protection unless a leakproof system is maintained. An entirely leakproof system is not obtained easily at all times, as every anesthetist knows. Furthermore, respiratory obstruction or some other emergency may occur which necessitates flooding the system with oxygen. The non-flammable mixture, thus, will be converted to a
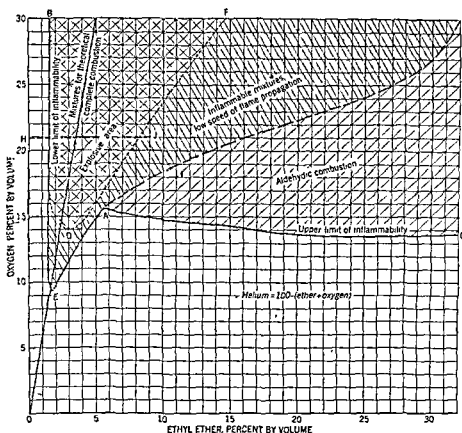
FIG 5.26. Graph illustrating range of inflammability of ethyl ether, helium, oxygen mixtures. The lıne BE defines the lower limits of inflammability From *Anesthesia and Analgesia*, 21:121 (June) 1942.) (Courtesy of Dr. G. J. Thomas, Dr. G W. Jones and *Anesthesia and Analgesia*.)

flammable one since the addition of oxygen immediately brings the concentration into the flammable range. During an operation the anesthetist is concerned primarily with and devotes his undivided attention to the manner in which the patient responds to the drug being administered. Whether or not a flammable mixture is present often becomes a secondary consideration. The mixture the anesthetist uses in adapted to the *patient and not the patient to the mixture*. For this reason, the use of quenching agents has been found impractical and has not received widespread acceptance as a method of preventing explosions.

QUENCHING EFFECTS OF HYDROCARBON GASES

Hydrocarbon gases exert some quenching effect also. Woodbridge and others noted that the upper limit of flammability of a mixture of ethylene, cyclopropane and oxygen is lower than either the limits of an ethylene-oxygen mixture or a cyclopropane-oxygen mixture. A similar quenching effect occurs when hydrogen is added to cyclopropane-oxygen mixtures.

Studies of the quenching effects of inert gases are valuable as well as interesting. To date, however, quenching agents have been of little practical value
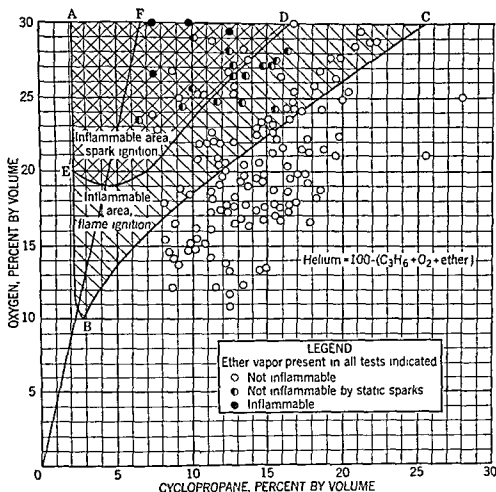
Fig. 6.26. Graph illustrating limits of inflammability of cyclopropane, ether, oxygen, and helium mixtures (From *Anesthesia and Analgesia*, 21:121 (June) 1942.) (Courtesy of Dr. G. J. Thomas, Dr. G. W. Jones and *Anesthesia and Analgesia*.)

for preventing fires and explosions during clinical anesthesia.

Sources of Ignition Causing Anesthetic Explosions

Flammable mixtures are ignited by flames, sparks or incandescent hot bodies. The types of ignition sources which initiate combustion of anesthetic mixtures are (1) Sparks resulting from discharges of static electricity. These cause more explosions than any other source of ignition. (2) Sparks from electrical equipment due to defective wiring,

faulty plugs, motors, x-ray units, diathermy machines and so on. (3) Open or naked flames. Cigarettes, gas burners and alcohol lamps are the most common sources. (4) Incandescent objects, such as cauteries, hot filaments, heating pad cords, and defective bulbs in endoscopic instruments. (5) Percussion sparks. These are due to mechanical friction or to the striking together of ferrous objects. Iron and steel are notorious for causing percussion sparks. (6) Spontaneous combustion. This may result from the catalytic action of metals, metal oxides or the

presence of impurities in drugs whose flashpoints or ignition temperatures are low. (7) High temperatures resulting from adiabatic compression of gases (Chap. 1).

STATIC ELECTRICITY

Inasmuch as static electricity causes the majority of anesthetic explosions, this subject merits some detailed discussion.

NATURE OF STATIC ELECTRICITY

In previous chapters it has been stated that atoms are composed of electrons, neutrons and protons. The electrons move about protons and neutrons in a planetary fashion. Electrons in the outermost orbit of an atom may be detached from the atom giving rise to various physical phenomena, of which static electricity is one. When two dissimilar materials are placed in contact with each other, these detachable electrons shift across the interface from one body to the other. If the interface is viewed microscopically the active points of contact are seen to be few and far between, even though grossly the two surfaces appear to be in intimate contact. Relatively speaking, the number of electrons involved in the shift from one body to the other is small. This is fortunate, otherwise, static electricity would be a greater problem than it is. The direction in which the electrons move depends upon the substance involved. For example, if glass is placed against sealing wax and both bodies are pulled apart, the electrons migrate from the glass to the sealing wax. In a listing known as the triboelectric Series (Table III.26) substances are arranged in the order of the direction of migration of electrons.

CONDUCTORS AND NON-CONDUCTORS

In some substances, particularly metals, electrons move from atom to atom with ease. In others, such as those composed of rubber, glass or plastics, the molecular structure is such that the movement occurs with difficulty. Substances through which electrons pass easily are referred to as *conductors*. Those through which passage is difficult are known as *non-conductors* or *dielectric substances*.

DEVELOPMENT OF STATIC CHARGES

The pulling apart or rubbing together of two dissimilar materials which are in intimate contact, if one or both is non-conductive, causes some of the electrons which have shifted to be trapped on one of the bodies. When both substances are conductors, the electrons pass back to their respective atomic positions before the separation of the two bodies is complete. None of the electrons are trapped (Fig. 7.26). The tendency is always to achieve electrical neutrality and for the electrons to return to their respective positions, even though there is such an accumulation of electrons on a body when a permanent separation is attempted or achieved. The non-conductive nature of a substance accounts for the sluggishness of the movement and the separation of electrons. Thus, in the case of non-conductors one body acquires a surplus of electrons and one develops a deficiency (Fig. 8.26).

TABLE III.26

TRIBOELECTRIC SERIES

Each substance becomes positively charged if rubbed against any substance below it.

Asbestos	Silk	Sealing wax
Glass	Aluminum	Ebonite
Mica	Paper	Ni, Cu, Ag, brass
Wool	Cotton	Sulphur
Cat's fur	Woods, iron	Pt, Hg.
Lead		Rubber
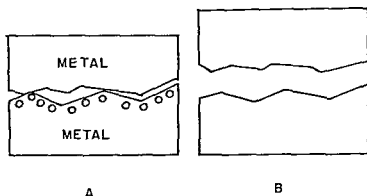
Fic. 7.26. (A) Two conductors in close approximation. Note that microscopic appearance would show point of contact at scattered intervals. Electrons have migrated from the upper to the lower piece. (B) The conductors have been pulled apart. The electrons have found their way back to their original body.

POSITIVE AND NEGATIVE CHARGES

Since electrons are units of negative electricity, the body acquiring the surplus has an excess of *negative electricity* and is referred to as being *negatively charged.* The body which has a deficiency of electrons is positively charged. Whether or not a body becomes positively or negatively charged depends upon its chemical nature and the position of the substance in the triboelectric Series. *The number of electrons acquired by a body is referred to as a charge.* The presence of a positive charge on a body indicates that another body has acquired electrons and has a negative charge. A charge of one sign cannot develop without the simultaneous development of *one of opposite sign on another body.* The trapped electrons on the negatively charged body will pass back to the positively charged one if given the oppor-
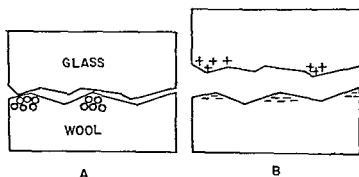
Fic. 8.26. (A) Two non-conductors in close approximation. Electrons have migrated from the glass to the wool. (B) The bodies have been drawn apart, but due to the non-conductivity the electrons have not passed back into the body from which they originated. The glass is deficient in electrons and, therefore, positively charged. The wool has an excess and is, therefore, negatively charged.

tunity. This is accomplished by placing a conductor between the bodies. Electrical charges separated by non-conductors repel or attract each other and, therefore, exert forces on each other. As is the case with magnetism, charges of like sign repel; those of opposite sign attract each other. Thus, electrons on two negatively charged bodies tend to repel each other. Two charged bodies separated by air retain their charges because air is a non-conducting substance and insulates them.

DEVELOPMENT OF STATIC CHARGES

Charges of electricity separated by non-conductors are at rest and, therefore, are called *static charges*. A flow of electrons from atom to atom produces a *current of electricity* or *dynamic electric-*ity. Placing a conductor between two static charges of opposite sign, permits the electrons to flow from the negatively charged to the positively charged body and achievement of electrical neutrality. As the electrons pass from the negatively charged body to the positively charged one they are in motion and are no longer static although the motion is for an instant. The presence of static charges may be detected by means of an *electroscope* (Fig. 9.26).

RESISTANCE TO THE PASSAGE OF ELECTRONS

All substances conduct electricity, to a certain degree, and also offer some resistance to the passage of electrons. In other words there is no such thing as an *absolute non-conductor* or a *perfect con-*
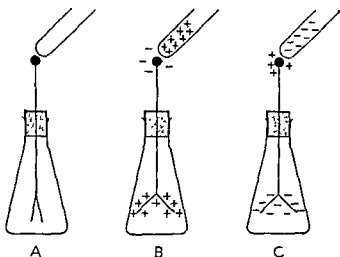
FIG. 9.26. The gold leaf electroscope consists of two slender strips of gold foil suspended from a metal rod passing through an insulator terminating in a knob. The device is enclosed in a glass vessel. The knob is stroked with a non-conductor which imparts a charge to it and the gold leaf. The leaves separate because like charges repel. Such separation is indicative of the presence of a charge. The amount of separation is an index of the magnitude of the charge. In the neutral position (A) the leaves are close together. A positively charged body induces a negative charge (B) and vice versa (C).

ductor. Substances which offer little resistance are used for conductors. Those which manifest a high degree of resistance are used for insulating and keeping electrical charges apart. The degree of resistance to the passage of electrons is expressed in units called *ohms.* The resistance of non-conductors is sometimes so great that a larger unit called a *megohm* (1,000,000 ohms) is necessary. Resistance ordinarily is measured with an instrument known as an *ohmeter.* High resistances, such as those encountered in the study of *electrostatics,* are measured with a device called a *"megger."* The word "megger" is an abbreviation of the word *megohmeter.* The "megger" utilizes currents of high potential (as many as 5000 volts) since it measures high resistance and high voltages are necessary to force the electrons through the body to be tested.

QUANTITIES OF ELECTRICITY

The quantity, or number of electrons, which accumulate or are removed from a body is referred to as the *charge.* Quantities of electricity are expressed in either one of two units, amperes or coulombs. Both terms have reference to the number of electrons present on a body. A *coulomb* is a standard electrical unit used to indicate a unit number of electrons (1,000,000,000 electrons). A charge of one coulomb passing a particular point in a conductor in one second is called one *ampere.* The ampere, therefore, takes into consideration the element of time, and indicates the *rate* of flow of electrons.

POTENTIAL

Charges acquire voltage or potential. *Potential* refers to the magnitude of the force tending to reunite the electrons

with atoms which have been deprived of and are deficient in electrons. The magnitude of the potential of two static charges is proportional to the amount of work or energy required to separate them. When the electrons resume their former atomic association this energy is released.

The entire situation of volts, amperes and ohms is comparable to the flow of water through a pipe. The resistance or friction to the flow of water depends upon the diameter of the pipe. This is comparable to the number of ohms of resistance a conductor offers to the passage of the current. The pressure forcing the water through the pipe is comparable to the *voltage.* The volume of water flowing through the pipe in a given time interval is comparable to the amperage. The forces of attraction or repulsion between two charges is equal to the products of the two charges divided by the square of the distance between them. The changes in potential or voltage caused by varying the distance between the two charges is referred to as *potential gradient.* The forces or repulsion of like charges are of the same order of magnitude as those which develop when unlike charges attract each other.

SIZE OF STATIC CHARGES

Charges of static electricity which develop in operating rooms by ordinary every day activity are small. In other words, relatively few electrons are involved in the build-up of static charges compared to the number involved when an electric current passes through a wire. The charge, however, may have an extremely high potential. In other words, the voltage developed in the separation is extremely high. Stroking a non-conductive breathing bag of an anesthetic ap-

paratus several times manually may generate a charge of small magnitude but of high potential. The potential may be in the order of 4000 or 5000 volts. When charges of static electricity are neutralized and electrons return to their respective atoms, nothing is lost, gained or destroyed. The electrons merely have resumed the atomic association present prior to the separation of the two bodies. The energy utilized to separate the electrons, however, is converted into heat (spark) as the potential is reduced to zero.

CAPACITATORS

Charges of static electricity develop principally on non-conductors. It is difficult to charge two conductors which are in intimate contact by separating them. The charge, once formed, remains on a body until neutralized. It is possible, however, to charge or add electrons to an *insulated* conductor. Two oppositely charged conductors separated by a non-conductor (insulator) form a capacitator. This is more commonly called a *condenser*. A capacitator stores electricity. In other words, it holds electrons. The quantity of electricity held by a capacitator is measured by a unit called a farad. A *farad* of electricity is equivalent to one coulomb of electricity—a sizeable number of electrons. The quantities of electricity ordinarily present on most condensors are only a fraction of a farad, therefore, the terms *micro-farad* and *micro-micro-farad* have been introduced to express these small quantities.

The voltages developed by a static charge are usually very high. The volt is not adequate for designating the magnitude of such a charge. Therefore, a larger unit called the *kilovolt* (1000 volts) is used to indicate such charges.
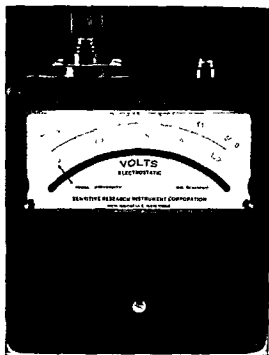
Fig. 10.26. A static voltmeter.

Voltages may be measured by a device called a *static voltmeter* (Fig. 10.26).

DIELECTRIC CONSTANTS

All substances, even the most resistant, possess some degree of conductivity. The measurement of this ability of non-conductors to conduct electricity is expressed by a unit called the *dielectric constant* (Symbol K) (Table IV.26). This constant is the ratio of the conductivity which the material possesses to the conductivity of air. In a vacuum this constant is arbitrarily designated as unity (1). Air is so poorly conductive that it is designated as having a constant of 1.

TABLE IV.26
DIELECTRIC CONSTANTS

Diamond	16.5	Carbon Dioxide	
Asphalt	2.86	(0°C.)	1.0009
Glass	3–10	Helium	1.00006
Mica	4–8	Air	1.00059
Paraffine	1.6–2.3	Nitrogen	1.00058
Beeswax	1.86	Oxygen	1.00053
Shellac	2.95–3.6		

Comparisons are, therefore, made with air as a reference. A substance which is 100 times more resistant to the passage of electrons than air has a dielectric constant of 0.001. The application of a particular voltage to a substance causes a certain amount of current to flow through it. As the voltage is increased the current which flows though increases proportionally. If the voltage is progressively increased a point is reached at which the electrons suddenly are able to break through. The substance no longer resists the passage of electrons at this point. The accomplishment of this breakthrough in a highly resistant substance requires an extremely large voltage, as a rule. The passage of the current at such a high voltage, however, causes a physical change in the substance. When the material no longer offers its original resistance to the passage of electrons and permits them to pass through, it is said to have "broken down." The voltage transfer, *after* the break down of an insulator, if this is a transparent material, such as a liquid or a gas, causes incandescence of the material. If the electrons pass through a gas a spark forms.

There is a distinction between resistance of a substance and break down voltage. The *resistance* of a substance is the ratio between the voltage applied to it and the current which flows. The *break down voltage* refers to the potential at which the material changes its properties and suddenly begins to conduct. As has been mentioned, air has a high degree of resistance and is considered a perfect insulator. It does, however, break down as two charges of opposite sign and high potential are brought closer together. A static charge of high potential which has accumulated on a conductor, isolated from conductors by insula-

tors, as for example, a metal stand on rubber casters, may be discharged through the air to an oppositely charged body. The insulation on electrical apparatus employing high voltages, such as an x-ray machine, may break down and permit charges to break through. This may happen particularly when the equipment has been in use for some time and the insulation has changed in structure and composition with time and use. *Thus, the presence of insulation on a device carrying a high potential is not absolute assurance of protection from formation of sparks.* One must consider such apparatus so constructed as hazardous if used in the presence of flammable anesthetics.

INDUCTION

The region about an electrically charged body is referred to as the electrical *field of force*. If an uncharged conductor is brought into an electric field of a charged body, a charge develops in the conductor. This charge is referred to as an *induced charge*. This charge is of opposite *sign from that of the electric field*. The manner in which this occurs is as follows: Electrons move easily through a conductor. Assume that an insulated body has acquired a positive charge and that an uncharged conductor approaches it. The free electrons of the conductor, of which the conductor has many, are attracted towards the portion of the conductor nearest the positively charged body (Fig. 11.26). The part of the conductor most remote from the positively charged body will, therefore, be deficient in electrons and be positively charged. The separation of positive and negative charges in an uncharged conductor when such a conductor is brought into an electric field is
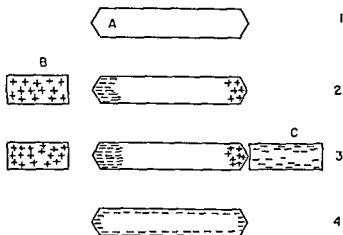
FIG. 11.26. Charging by induction. The insulated conductor (A) which is neutral (1) is approached by positively charged body (B). Electrons shift towards (B) causing one end to be positively charged and one negatively charged (2). A second body negatively charged (C) approaches and makes contact with the positively charged end (3). Electrons pass from (C) to (A). (B) Moves away from (A). The influence is lost and (A) remains with an excess of electrons and, therefore, negatively charged (4).

called *induction* or charging by *influence*. Such a situation may develop in an operating room when a person who is positively charged but who is isolated from the floor by wearing rubber soled shoes approaches the foot end of an operating table. The table is an excellent conductor but is isolated electrically from the floor by insulated casters. The electrons in the table are attracted towards the individual and a negative charge develops in this portion of the operating table. The head end, which is most remote from the charged individual, will be deficient in electrons and be positively charged. A third body, one which is negatively charged, approaching the head end of the table (the positively charged end) could be responsible for the formation of a spark if the air gap is shortened sufficiently. If the charged body remains at a distance in the vicinity of the operating table, the charges will remain on the table until the influence has been removed when the person walks away from the table. Such a charge held on an object by another charged body is referred to as a *bound charge*.

DISTRIBUTION OF CHARGES

A charge becomes distributed uniformly over the surface of a spherical conductor (Fig. 12.26). In an irregularly shaped conductor, say for example an ovoid one, the charges crowd at the points of most curvature (Fig. 13.26). The charges are repelled since they are alike and move apart. Thus, each end of the ovoid body bears the charge. Charges of static electricity on irregular bodies tend to concentrate at sharp points or at points of greatest curvative. A different situation exists if the body is a non-conductor, however. The distribution of the charge is not predictable. A non-con-

ductive rubber breathing tube which has been moistened both inside and outside may set up the same situation as is found in a capacitor. Charges of opposite sign may accumulate on each surface separated by the rubber which is a dielectric substance. If the charges are of high potential they may break through some point in the rubber and cause a spark.

A positive charge on a body cannot be removed from one area to another without moving the body carrying the charge to the new locality. The presence of a positively charged body in an area indicates that a body with a negative charge is nearby or has been moved from the electrical field. Likewise, the presence of a positively charged body indicates removal of one with a negative charge.

GROUNDING OF STATIC CHARGES

The earth acts as a reservoir or storehouse for electrons. Electrons are supplied from the earth when needed to neutralize a positive charge and are absorbed by the earth when an excess is present, as is the case when a negative charge is present on a body. The earth, therefore, is capable of acting as either a negatively or positively charged body depending upon the charge of the body

FIG. 12.26. The charge on a sphere is uniform and on its outer surface.

FIG. 13.26. The charge on an ovoid body is most concentrated at its point of least curvature.

in proximity to it. A positively charged body which comes into contact with the earth has the charge neutralized by the electrons drawn from the earth by the force of attraction of the positive charge (Fig. 14.26). The earth to cloud movement of charges of static electricity which occurs when lightning flashes is explained by this behavior of electrons.

ENERGY OF SPARKS

The sparks caused by rapid neutralization of electrostatic charges in operating rooms are of extremely short length and of brief duration. The energy dissipated in such sparks is sufficient to raise the temperature of the gases in the vicinity above the kindling point of most flammable mixtures. Sparks as short as 0.05" or 0.1 mm. may ignite flammable mixtures of hydrocarbons or ether mixed with air. Mixtures composed of higher concentrations of oxygen and a flammable agent may be ignited by even shorter sparks. The minimum length of a spark which may ignite an oxygen rich mixture is estimated to be 0.005" or 0.01 mm. These sparks are too small to be seen with the naked eye. The amount of electrical energy in a static spark, expressed in terms of heat generated, which ignites an anesthetic mixture may be as little as 1 millionth of a gram calorie. This amount of electricity is re-

Fig. 14 26. The earth is a storehouse for electrons supplying electrons to neutralize a positive charge (A) or absorbing an excess from a negatively charged body (B).

leased almost instantaneously through a very small volume of gas mixture. It is, however, sufficient to heat the minute volume of gas through which the electrons pass to temperatures as high as 1000°C. The faster the energy is released and the smaller the volume of gas through which the electrons pass, the hotter the spark and the lower the minimum energy necessary to ignite a particular flammable mixture.

ANTI-STATIC MEASURES

Since static electricity is being formed constantly as a result of unavoidable activity of operating room personnel, there is little that can be done to prevent its formation. Therefore, measures must be instituted which favor its rapid dissipation and prevent its accumulation on insulated bodies. The answer to the antistatic problem lies in *eliminating nonconductors* from anesthetizing areas and inter-connecting all conductors to provide a continuous path through which electrons may flow freely. In other

words, all objects in an operating room should be at the same electrostatic potential. In present day practice this is accomplished by installing conductive flooring and establishing good electrical contact between all objects in the room and the floor. Objects not in contact with the floor must be intercoupled with those which are, so that a uniform homogenous pathway is established through which electrons move with ease. Thus, every object in an operating room must possess sufficient conductivity to cause rapid dissipation of charges. Isolation and accumulation of charges on any one object is impossible, if all objects are conductive and inter-connected electrically.

Certain substances possess a greater degree of conductivity than others. Silk, wool, synthetic fabrics, rubber and plastic objects are non-conductive and should never be permitted in operating rooms. Cotton sheeting is also non-conductive but it is more conductive than silk, wool or synthetic fabrics. A cotton sheet in direct contact with the skin or with a

conductive surface, such as an operating or instrument table, may acquire a charge. The charge, however, is dissipated gradually and with sufficient rapidity so that it does not become a hazard. Casters, wheels, tires, stool leg tips, rubber accessories on surgical and anesthetic equipment, such as breathing bags, face masks, delivery tubes and valve housings and so on must be conductive.

In due time many objects, because of wear, accumulation of non-conductive films of dirt, waxes and other substances, or because of changes in composition or crystallization of the inner structure, become non-conductive. All conductive accessories, such as bags, must be tested frequently for conductivity. Whether or not a substance is considered to be a conductor or an insulator is a relative matter. Silk, for example, holds a charge for a longer period of time than cotton. Both are non-conductors, but cotton is less so than silk.

No device is available which can be used to prevent the accumulation of electrostatic charges. An instrument known as a *staticator*, introduced some years ago, detects the occurrence of an electrostatic discharge. It does not prevent the accumulation of static charges as has been erroneously believed. When a charge is rapidly dissipated from a body electromagnetic waves are radiated from that area. The staticator acts as a receiver for these waves, and like a radio, converts these waves into sound. The intensity and the rate of dissipation of the charge may be estimated by the quality of the sound emitted from the receiver. The staticator in no way prevents the accumulation of an electrostatic charge. It merely indicates that a static charge was present and has been neutralized.

The origin of the sound emitted by a staticator is similar to that heard in a radio shortly after a flash of lightning is sen. The radio does not prevent the accumulation of the static charge which caused the lightning. The staticator, likewise, does not prevent the accumulation of the charge or the spark.

CONDUCTIVE FLOORS

Rubber, linoleum, marble, ceramic, porcelain, concrete and concrete terrazzo are insulating substances. Consequently, charges of high potential may develop when persons walk upon or objects are moved over floors composed of these substances. The degree of insulation of each of these floors, however, is a relative one. Concrete terrazzo has the least resistance and, therefore, is the most conductive. Resistances which have been reported in floors composed of these materials are as follows: Porcelain—5000 megohms, terrazzo—12,000 and concrete —4000. Floors composed of substances which have some degree of porosity, such as concrete terrazzo, conduct better when old than when new. As time passes, the myriads of fissures and crevices between the chips in the mass become filled with moisture and electrolytes. The conductivity is thereby increased. Terrazzo floors installed with closely spaced bronze or brass strips (approximately 4" apart in a grid-like fashion) are effective in causing the dissipation of charges induced by walking or pushing objects over them. The material in the area between the metal strips, obviously, is far less conductive than the metal. The entire grid is installed as a unit and is continuous throughout. If measures are taken to ground all objects in an operating room to the grid, everything in the room will be at the same potential.

The conductivity of terrazzo floors may be increased by incorporating carbon in the form of *acetylene black* in the concrete. Efforts to confer conductivity to cement floors by the addition of *powdered metal filings* have been unsuccessful because the particles fail to touch each other and form a homogenous chain. Acetylene black, if thoroughly mixed in the concrete, produces a homogenous filamentary conductive path throughout the floor. Magnesium oxychloride may also be incorporated in the mixture to confer conductivity. Linoleum, vinyl plastic and conductive ceramic tile are made conductive by the addition of carbon also.

LIMITATIONS OF USEFULNESS OF CONDUCTIVE FLOORS

The installation of a conductive floor by no means insures freedom from the hazards of static electricity. A false sense of security is easily developed unless the limits of usefulness of a conductive floor are understood. The resistance a floor will have after the concrete has set cannot be predicted. Floors which have adequate resistance to dissipate charges when first laid may lose a good deal of their conductivity and become resistant after varying periods of time. Many concrete terrazzo floors containing carbon black have lost their conductivity after a period of years due to the development of minute cracks, loss of moisture or change of crystalline structure. Films of wax, dirt and soaps may increase resistance of any floor, no matter how conductive it is, by reducing conductivity at the surface. Waxes for flooring should be of the conductive type. Conductive waxes or paints on non-conductive floors are not substitutes for conductive flooring. Non-conductive floors may be cov-

ered with conductive linoleum or conductive vinyl plastic tile.

DETERMINATION OF CONDUCTIVITY OF FLOOR

The effects of aging, trauma, and washing with detergents on floor resistance are not fully understood. Therefore, a periodic test is essential to determine whether or not the conductivity is within the recommended limits. The resistance of a floor is determined with a "megger." Two foil coated, 5 pound cylindrical, electrodes with a surface area of 5 sq. in., are placed three feet apart on the floor. Usually a 500 volt megger with a calibrated range between zero to 1000 megohms is used (Fig. 15.26). The resistance should be not less than 25,000 ohms and no more than 500,000 ohms anywhere in the room with the electrodes three feet apart.

An acceptable floor possesses sufficient conductivity to permit the neutralization of charges on operating room furnishings and personnel at a faster rate than they develop. A floor with zero resistance would be ideal from the standpoint of dissipation of static charges but dangerous from the point of view of shock from power lines. The floor must possess some resistance to prevent sparks or shocks should accidental contact be made with electric power lines, exposed wires or defective electrical equipment. This is the chief objection to the suggestion that floors be made entirely of metal. Floors having a resistance of more than 25,000 ohms safeguard against such accidents. The practice of grounding floors by means of heavy conductors to water pipes or metal plates buried in the ground is obsolete, dangerous and unnecessary. A brass or bronze grid strip in a terrazzo floor should have isolation
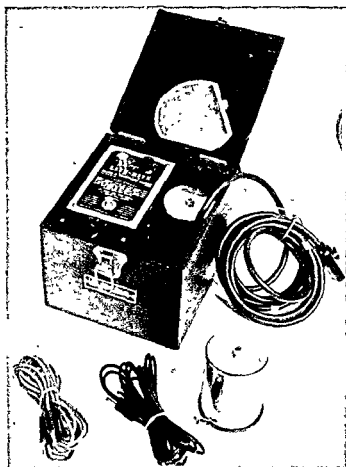
FIG. 15.26. The "megger" used to determine resistances of equipment in operating rooms and conductivity of floors. The circular weights are placed three feet apart on the conductive floor. Floors having resistance of more than 0.5 megohm or less than 25,000 ohms are not acceptable. (Courtesy W. E. Anderson Co., Kansas City, Mo.)

transformers interposed between it and the ground to prevent direct grounding in the event of short circuiting. The most important feature of a conductive floor is that there be good point to point contact through the floor. Shoes, leg casters and other items ordinarily making contact with the floor should possess no more resistance than that possessed by the floor. If these conditions be fulfilled and all objects in the room are in contact with the floor, a zero potential will exist between all objects in a room. Charges, therefore, cannot accumulate on any object. The only un-neutralized charges which might require grounding are those which remain in the room when the object or person causing them leaves the room. Conductive waxes and paints applied to non-conductive surfaces do not satisfy the requirements of conductivity or take the place of a conductive floor.

INTERCOUPLING

Any device which connects two or more insulated bodies to facilitate the passage of electrons between them may

be considered to be an *intercoupler*. The conductive floor is actually a large scale intercoupler. The type intercoupler most familiar to anesthetists is the one introduced by Horton. This device permits a free interchange of electrons between electrically isolated objects in an operating room. The Horton unit is composed of 5 copper leads, or wires, each of which is fixed to a central body having a resistance of 1 megohm. Electrical clips are attached to three of the leads and wristbands to the remaining two. One clip is attached to the anesthetic apparatus, one to the operating table and one is placed in contact with the ground or the floor. One wristband is placed around the wrist of the patient and the other around the wrist of the anesthetist (Figs. 16.26;

17.26). Thus, these five objects, the floor, the anesthetist, the patient, the operating table and the anesthetic apparatus are inter-connected so that there is a resistance of one megohm between each of them. The resistance is low enough to permit rapid and easy equalization of electrostatic potentials between the inter-connected objects. The resistance is of sufficient magnitude to prevent a serious electric shock should one of the intercoupled bodies accidently come into contact with an electric power line. The resistance allows equalization of potentials between two charged bodies of unequal electro static potentials in approximately 1/100 of a second. The intercoupler was introduced primarily to be used in hazardous areas without conduc-
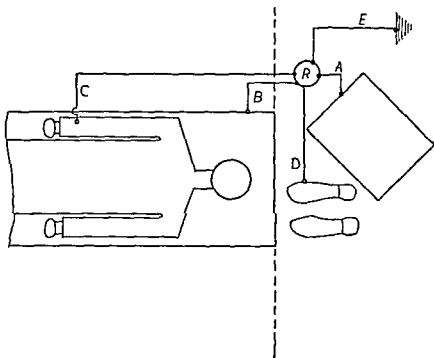
Fig. 16 26. Schematic diagram of the "hook up" of the intercoupler: (R) is a resistance of one megohm connected to the various leads. Lead (A) is connected to the machine (B) to the operating table; the wrist band of lead (C) is wrapped around the wrist of the patient, (D) is wrapped around the left wrist of the anesthetist, and (E) is clipped to the ground.

tive flooring. Unlike the conductive floor, an intercoupler provides a conductive path between five objects in the operating room. Other objects are not interconnected. The requirements that all objects be conductive and inter-connected is only partly fulfilled. Objections to the intercoupler are that it is awkward, cumbersome, unwieldy and that there is a frequent tendency for personnel to overlook connecting it properly. The intercoupler may fail to function properly because corrosion of the terminals, grease, dirt or other non-conducting films prevent good contact with the isolated bodies. The lead wires in the terminals may become twisted and frayed or broken beneath the insulation and may not conduct even though they appear to be in good order.

WET TOWEL INTERCOUPLING

In the absence of conductive flooring, and when the Horton intercoupler is not available, intercoupling may be improved by the use of wet towels. Several towels, moistened with water or saline are used. One is arranged so that it extends from the exposed bare shoulder of the patient to the metal portion of the operating table (Fig. 18.26). Another is placed between the base of the operating table to the base of the anesthetic apparatus. The third is placed from the base of the operating table to the foot of the anesthetist. This technique referred to as *"wet toweling intercoupling"* is a makeshift arrangement but does afford an ample degree of protection in emergency situations. Obviously, it is not a substitute for the conductive floor nor is it as desirable and as effective as a *properly functioning* Horton intercoupler.
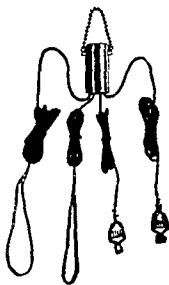
HUMIDIFICATION

The erroneous impression that static electricity will not develop if the room atmosphere is humidified is widely disseminated. A high atmospheric moisture content favors dissipation of static charges, but does not prevent such charges from forming. Charges of static electricity may accumulate on non-conductors surrounded by highly humidified atmospheres. Explosions of anesthetic mixtures can and have occurred in the presence of high humidity. Water vapor, contrary to general existing impressions, is a poor conductor of electricity. The addition of water vapor to a gas does not increase its conductivity. Actually, the conductivity of air, instead of being increased is decreased slightly by the presence of water vapor. The beneficial effects of humidity are largely due to the *leakage effect* caused by films of moisture adsorbed to the surfaces of insulating materials. Most objects are coated with electrolytes from sweat of the hands, soap, water and other sources. These electrolytes in the film of moisture im-

Fig. 18.26. Photo—Wet towel intercoupling. (Courtesy Dr. George Thomas.)

part a varying degree of conductivity to the surface. These films of moisture and electrolytes make the separation of electrons more difficult when objects in contact with each other are pulled apart. In other words, a charge develops with greater difficulty on a non-conductor in a humid atmosphere. However, this tendency varies with the nature of the non-conductor. The surface resistance of most non-conductors ordinarily found in operating rooms becomes less and less as the humidity increases. The usual humidity recommended is 55%–65% for dissipation of most charges. The surface resistance of such highly non-conductive substances, such as paraffin, silk, wool, nylon and plastics does not change appreciably even when exposed to atmospheres 100% saturated with water vapor.

They are, therefore, capable of developing and tenaciously holding charges and, therefore, should be excluded from hazardous areas at all times.

A period of time, usually several hours, is required for an equilibrium to be established between the water content of a semi-conductive material and the humidified atmosphere. During the time equilibrium is being established static charges may not be dissipated if the semi-conductor has previously been in a dry atmosphere. In order for humidification to be effective, the moisture content must be maintained at a constant, sustained level. Whatever protection a humid atmosphere affords is of questionable value when humidifying systems operate at irregular schedules. Equipment should operate continuously.

EFFECT OF CARBON DIOXIDE

Carbon dioxide combines with water to form carbonic acid which is an ionizable electrolyte. The conductivity afforded by the ions furnished by the carbon dioxide normally present in air (0.03%) has been shown, by calculations, to be of little consequence as far as aiding in dissipation of static charge is concerned. The electrolytes dissolved in the mixture on the surface of most objects furnish far more ions than does atmospheric carbon dioxide. The washing of air by air-conditioning equipment does not materially reduce the carbon dioxide content unless the wash water is alkaline. Thus, even if carbon dioxide were of value air-conditioning systems would not decrease this effect.

ANESTHETIZING AND HAZARDOUS LOCATIONS

A distinction is made between an *anesthetizing location* and a *hazardous location*. The term anesthetizing location refers to areas of a hospital in which combustible anesthetics are administered to patients in the course of treatment. Operating rooms, delivery rooms, utility rooms and other areas used for induction and maintenance of anesthesia are placed under this category. A *hazardous location* is one in which flammable substances may be present and cause a fire or an explosion. Rooms used for storage of combustible anesthetics and areas through which patients are transported who have been anesthetized are considered hazardous locations. Recovery rooms are neither anesthetizing nor hazardous locations unless specifically used for the administration of anesthetics. Corridors leading from operating rooms to recovery rooms are considered hazardous locations. It is doubtful that the breath of a patient recovering from anesthesia en route from an operating room may ignite unless he has swallowed gas and belches it. Nonetheless, strictest precautions should be taken at all times, even in the corridors.

PRACTICAL RECOMMENDATIONS

ANESTHESIA APPARATUS

LEAKS

Numerous recommendations have been proposed for the prevention of ignition of anesthetic mixtures. The majority of explosions have occurred at the site of leaks in closed systems. Most leaks occur at the mask and this is the point of greatest danger. Explosions are alleged to have occurred by igniting of mixtures within a closed system in which there was no evidence of a leak. However, with the exception of a few questionable isolated cases all have occurred when a leak or a break in the system was known to have existed. Attempts to maintain a leakproof system should be made, not only from the standpoint of administering good anesthesia, but also from the standpoint of eliminating the fire hazard completely. It is often argued that *explosive mixtures leaking from closed inhalers are diluted below the flammable range as they escape into the room air*. It has been estimated that mixtures escaping from points of leakage are diluted below the flammable range after diffusing a distance of approximately two feet. Theoretically, the danger of ignition does not exist beyond this radius and a hot body outside this zone should

cause no ignition. However, one does not have this unreserved assurance and should, therefore, err on the side of conservatism and designate an area far beyond this radius as a hazardous one.

USE OF CLOSED SYSTEMS

Caution should always be exercised in connecting and disconnecting masks, breathing bags, or breathing tubes. Handling of these objects may produce static charges which subsequently produce a spark on recoupling thereby causing ignition of the mixture at the point of disconnection. Connections should be made and broken while each part is in the operator's hands. Since many explosions occur at the mask, contact should be maintained with the patient's chin at all times. When the hand handling the mask is being shifted the anesthetist should contact the chin with the other one first. The carbon dioxide absorption technique should be used for the administration of flammable anesthetics whenever possible so that a completely closed system is used. As a precaution, the anesthetist should touch the patient and gas machine before releasing vapors and gases into the inhaler. Masks should be placed in contact with the patient's face after having first been connected with the apparatus. Non-flammable mixtures should be allowed to flow until all connections are made and a leakproof system has been established. Oxygen should be used for the first few breaths and then the flow of flammable mixtures commenced.

CONDUCTIVE RUBBER

Impregnation of rubber with finely divided carbon decreases its resistance and renders it conductive. Unfortunately such treatment reduces the distensibility and durability of the rubber and makes it ponderous. Nevertheless, conductive rubber is essential for the sake of safety. All masks, tubings, breathing bags and other rubber items should be of the conductive variety to insure a pathway of low resistance from one item to the next. Non-conductive rubber coated with conductive rubber is not satisfactory. Mattresses, pads, pillows, arm boards and similar items on operating tables or recovery room rollers should be covered with conductive rubber sheeting. Casters, tires and recovery room beds and stretchers, stool leg tips should be composed of conductive rubber. Breathing tubes should be of the corrugated conductive rubber type. The use of plain, non-corrugated breathing tubes with a wire spiral incorporated in its walls is hazardous. The wire may break so that the two free ends may come together as the tube is handled and cause a spark should the surrounding rubber inadvertently acquire a charge. Explosions which have occurred in an entirely closed system have been ascribed to this cause. Conductive rubber may lose its conductivity with time due to the separation of the carbon particles as the rubber is stretched from use or to structural changes in the rubber. Therefore, these items should be tested for conductivity periodically with a "megger."

Adhesive is non-conductive. Charges of high potential may develop when adhesive is stripped from a roll. Sparks may be seen if this is done in a darkened room.

GROUNDING

Objects which are moved in and out of operating rooms should make electrical contact with the floor or should be grounded with some metal device. Chains are usually used for this purpose. Chains should be of non-ferrous metal

of the open-link type. Bronze or brass or similar alloy are used because they do not cause percussion sparks. The ball or beaded type of chain is not satisfactory because contact between each link is not assured due to the accumulation of fibers, lint, dirt or wax. Furthermore, the inner parts are inaccessible for cleaning. Bronze plated steel chain is not acceptable. Chains should make as long a line of contact with the floor as possible. This may be done by fastening each length, preferably with bolts, diagonally beneath the piece of equipment. Contact should be made at all times with the conductive floor or the metal strip, if the terrazzo is not impregnated with carbon black. Such chains should be cleaned periodically to remove dirt, wax, grease and soap films to assure good contact with the floor. Chains touching high resistance floors without an inlaid metal grid may or may not be of value for dissipation charges. Much of this depends upon the resistance of the floor. All floors afford some leakage of charge. The more resistant the floor the slower the dissipation will be. However, such an arrangement cannot be relied upon for safety since the floor is not conductive and intercoupling should be used.

The use of objects of ferrous metals, such as buckets, stools, etc. in any situation in which two metal surfaces may strike each other creates a fire hazard because percussion sparks result from such contacts. Such surfaces which are apt to strike each other should be covered with conductive rubber.

WEARING APPAREL
FABRICS

Cotton is the most desirable, the least expensive and the most readily available substance for wearing apparel, drapes, sheets or other items composed of fabric

to be used in hazardous and anesthetizing areas. It possesses leakage powers at low humidities and does not produce or acquire any sizeable charge by frictional contact with other cotton objects, conductive rubber pads or instrument stands. All personnel should wear cotton uniforms. Persons wearing wool, silk, nylon and synthetic fabrics should not enter an anesthetizing location. Undergarments of silk, nylon, sharkskin or synthetic fabrics may be worn only if in direct contact with the skin. Underskirts not in complete contact with the skin cannot be used. Nylon socks may insulate the wearer even though conductive shoes are worn. The use of plastic covered items, such as arm boards, pads, pillows or plastic aprons and drapes should be avoided in all anesthetizing locations. Platforms should be made of metal coated with conductive rubber, and be grounded to the floor with bronze chains. Warming cabinets for blankets or gowns should be provided with a humidifier for keeping the articles moist. Dry blankets may lose their moisture and, therefore, their ability to dissipate electrical charges. Only cotton blankets should be used. Items composed of cloth which contain cotton, wool and a synthetic fabric should not be used. Anesthesia machines should not be covered with drapes even though such coverings are made of cotton. Gases may accumulate beneath them and be ignited by static sparks when the covers are pulled off.

SHOES

The soles of all shoes worn by persons coming into an anesthetizing location should be conductive. Every operating room suite should have a shoe tester (Fig. 19.26) of an approved design at some convenient location so that all per-
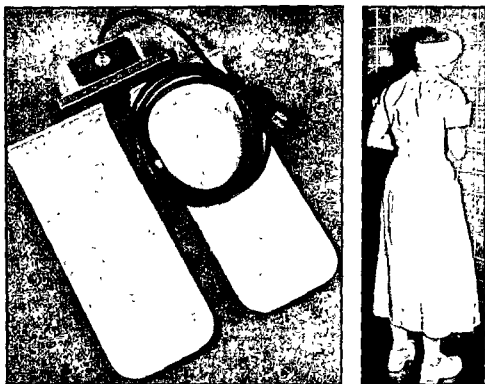
Fig. 19 26 Ohmeter for determining conductivity of shoes of operating room personnel. The instrument operates on ordinary 110 volt alternating current. When the resistance of the shoes exceeds one megohm the light does not show and the shoes are not considered safe. (Courtesy W. E. Anderson Co., Kansas City, Mo.)

sons entering the operating suite may test their shoes for conductivity. The resistance of the soles of shoes worn by all personnel should not exceed 1 megohm. A felt pad moistened with water or saline should be available next to the tester so that wax, grease and dirt may be wiped from the undersurface. Leather-soled shoes may be worn if they pass the conductivity test. Old leather shoes possess some degree of conductivity because the moisture and electrolytes in the perspiration permeate into the leather and decrease its resistance sufficiently to cause dissipation of static charges. Soles should be sewn onto the shoes. Shoes with exposed nail heads are not acceptable. The probability of a percussion resulting from the striking of a steel nail head against another metal and causing an explosion

is remote. Nevertheless, this recommendation is made by advisory groups on fire hazards and should be followed. Leather shoes may be non-conductive when they are first put on but after a period of time, as the moisture permeates into the leather, they become conductive. Conductive rubber slip-ons are available to make leather shoes safe. Brass nails or tacks at the bottom of non-conductive shoes are not acceptable because they do not cover a wide enough area. They would not come into contact with the grid of a terrazzo floor not impregnated with carbon. The dissipation of an acquired charge would be a matter of chance. Besides they may be dangerous to the wearer in the event inadvertent contact is made with a power line because of the low resistance in the metal.

ELECTRICAL EQUIPMENT

All electrical equipment, such as fixtures, wires and motors used in operating rooms and hazardous locations should be of the spark proof type. It should be given meticulous care and inspected regularly. All receptacles and plugs should be of the type which cannot accidently be pulled apart at an inopportune time. Receptacles should be of the explosion proof type if placed less than five feet from the floor. Conventional type (household) switches and receptacles may be used if placed five feet or more above the floor. All switchboard panels should be enclosed and installed outside the operating room whenever possible and should be five feet or more from the floor. All electrical wiring and equipment should conform to the recommendations made by the Fire Underwriters and the National Fire Protection Association. Conventional open motors, heaters, heating pads, x-ray machines, diathermy machines and similar equipment which might be the source of sparks or cause wires or similar metals to become incandescent should not be used in any hazardous or anesthetizing area.

TRANSFORMERS

Endoscopic instruments should operate on batteries utilizing currents less than 8 volts. Transformers are not acceptable unless they may be plugged in at the wall and the primary and seondary winding are isolated from each other by an insulator. The ordinary head lamp deriving power from transformers is, as a rule, flimsy in construction and not safe. Dental drills, orthopedic saws and similar items driven by electric power must be of an approved type if employed in the presence of flammable gases and vapors. The electrical power supplied to anesthetizing and hazardous areas should come through an *isolation transformer* which isolates the *circuits from the outside main feeder* power line.

GROUNDING OF ELECTRICAL EQUIPMENT

Electric lamps, motors, plugs and *other devices using the conventional* 110 volt current should carry a third wire for positive grounding to reduce the possibility of short circuiting and shocking of personnel. The grounding of electrical equipment, whether the equipment is of the approved or the conventional type, places the housing or casings at the same potential as that of the earth or of the conductive flooring. Should the insulation fail and contact be made with the outside or enclosure, such as the frame of a suction or a lamp, the danger of *shock and an external power spark is* minimized. Conduits, switch boxes, motor housing and similar items should also be grounded. *Isolation transformers* should be used when low resistance pathways are present from floor to ground.

CONDUITS AND SWITCHES

Conduits, switches and other electrical receptacles used in locations where flammable gases or vapors are administered should be explosion proof. *Explosion proof* conduits and enclosures consist of relatively small compartments having walls which are designed to withstand the pressure of an explosion occurring within the receptacle and prevent the passage of a flame to the outside if a *combustible gas within it* be ignited. The explosion proof receptacle isolates the gas in the receptacle from

the gas in the room. The flame is there-
by enclosed and limited to the confines
of the plug.

SWITCHES

A spark results when the connection
is broken each time a switch is turned on
or off. This occurs in all switches and
cannot be averted. Therefore, the con-
ventional household switches and lamp
sockets are hazardous in an operating
room unless located remotely from the
immediate vicinity of the combustible
substance and they are five feet above
the floor. Sparking also occurs in an ex-
plosion proof switch but causes no harm
because the contacts are isolated from
the gases in the room by a non-flamma-
ble, non-breakable vapor proof housing.
The gases in a conventional switch are
in direct contact with those of the room.
Mercury switches, likewise, are not ac-
ceptable because they too spark. Ad-
mittedly the elements are enclosed in a
sealed tube and the spark is isolated but
the tube is made of glass and is subject
to breakage in which case the gases in
the room may be exposed to sparks.

CORDS

Electrical cords on portable equip-
ment should be heavy duty type. Cords
should have multiple layers of insula-
tion to avert the possibility of sparking
caused by fraying of the insulation.
Cords should be discarded at the first
sign of wear of the outer insulating coat.
They should be arranged so that stretch-
ers and other portable equipment do not
roll over them.

MONITORING DEVICES

Monitoring devices utilizing various
electronic principles on the usual 110

volt type current, such as oscilloscopes,
electrocardiographs, and electroencepha-
lographs, unless designed for use in an-
esthetizing areas, are not safe to use with
flammable anesthetics. They may be
sources of ignition and should be placed
outside the operating room.

LAMPS

Lamps used in the operating room
should be of the vapor proof type, par-
ticularly when used within five feet of
the head of the patient. The bulb should
be shielded in a vapor proof enclosure so
that accidental spattering of water, se-
cretions or vomitus will not cause the
bulb to crack or burst. Small bulbs on
endoscopic equipment should be tested
periodically. Short circuiting of the fila-
ments may elevate the temperature
above the ignition temperatures of flam-
mable mixtures. X-ray viewing boxes
should exclude the atmosphere of the
operating room. Switches for ceiling
lights should be placed on the wall five
feet from the floor. Cauteries and high
frequency coagulating equipment should
not be used in areas where flammable an-
esthetics are administered.

GAS STORAGE AREAS

Gas storage areas should be regarded
as hazardous locations. Storage rooms or
manifold enclosures for oxygen, nitrous
oxide and other gases whose capacity
exceeds 1500 cu. ft. should be ventilated
to the outside of the building. Smaller
rooms may be ventilated in the conven-
tional manner. Such rooms or manifold
enclosures must be constructed of build-
ing materials having a fire resistance rat-
ing of at least one hour. They must not
communicate directly with anesthetizing
locations. Piping systems should not be

used for the distribution of combustible anesthetics. Flammable anesthetic gases should be stored separately from oxidizing and inert gases. A separate room should be provided for each of these two types of gases.

HANDLING CYLINDERS AND PIPE LINES

Cylinders should be stored upon racks of a non-flammable substance, preferably in the upright position. However, if placed upright they should be arranged so that they are supported and cannot be upset. Paper wrapping should be removed from cylinders before placing them in service. Oil, grease, flammable liquids and pastes should not come into contact with cylinder valves, regulator gauges or fittings. Regulator fittings and gauges should never be oiled. Fluorinated hydrocarbons or similar lubricants having a high flashpoint should be used for lubrication. Particles of dust, or dirt must be cleared from the outlet of each cylinder by "cracking" (momentarily opening the cylinder valve) the cylinder to avoid the possibility of a flash fire. Gases at high pressure, particularly oxygen, must not be admitted suddenly into a regulator to avoid the possibility of rupture of the diaphragm. The valve is best opened gradually. The main valve should be fully opened when a cylinder of a compressed gas is placed in use and closed at all times when not in use. The maximum pressure in a pipe line should not exceed 100 lbs. per sq. in. Pipe lines should be painted the same color as the cylinder of the gas to which it is connected. Pipes passing through tunnels should be labelled "Dangerous Gases." They should be isolated from cables.

REGULATIONS AND LAWS

A number of national agencies are interested in fire and explosion hazards. Most active of these are the National Fire Protection Association (N.F.P.A.), and the National Board of Fire Underwriters, the American Hospital Association and the Bureau of Mines. Recommendations made by these agencies are suggestions and not rules or laws. Many municipalities and some states have statutes, ordinances and rulings which the fire marshal and other officials enforce. Many of these laws are based upon the recommendations of the Fire Underwriters and the other bodies. The National Fire Protection Association is an incorporated body made up of almost 200 regional and local societies which meet periodically and formulate recommendations on fire prevention based on past experience. They customarily publish their recommendations in a small pamphlet which is revised each year or two.

VENTILATION OF OPERATING ROOMS

Whether or not an operating room should be ventilated has been the subject of much debate. Generally it is recommended that air be changed completely and not recirculated to prevent accumulation of flammable gases. However, diffusion occurs so rapidly that it is doubtful that any accumulation of flammable mixtures can occur. One pound of ether mixed with air yields 277 cu. ft. of a flammable mixture at ordinary room temperature and atmospheric pressure. This is a relatively small volume. Nonetheless, precautions cannot be too many and nothing must be overlooked.

Part III

BIOCHEMISTRY RELATED
TO ANESTHESIA

Introduction

ANESTHESIA interrupts physiological functions with effects which are far-reaching. Biochemical and pathological changes may occur in blood and tissues as the result of these disturbances. Much has been written about the effects of anesthetic drugs on tissues. In a number of instances, diametrically opposite views and interpretations are held by different investigators. This situation arises not because of inaccuracies in observations but rather from numerous, often uncontrollable variables which may enter into these studies. Anesthetic drugs may stimulate or depress the automatic nervous system, interfere with hormone and enzyme activity, depress metabolism, or interfere with gaseous exchange in blood and tissues. Disturbances of absorption and secretion may occur which may reflect themselves in electrolyte and fluid balance. Liver functions, most of which are biochemical, may be depressed. Physiological functions are so interrelated that often no single one can be considered individually but a group must be considered as a whole.

A factor frequently ignored but of extreme importance is the technique and depth of anesthesia. Oxygen lack, carbon dioxide excess, respiratory obstruction, environmental temperature and psychic state of the subject are incidents of anesthesia which have far-reaching influence on biochemical changes. Discrepancies exist between older and more recent experimental data. These may be due to the greater attention paid to details as well as to the technique of anesthesia in the newer experiments. Much of the reported data has been obtained during clinical anesthesia on operated subjects whose normal physiology is disturbed and who may already have profound biochemical changes as the result of disease. Naturally, these may not respond to anesthesia as do normal subjects. In the case of animal experiments, variations between individual subjects of the same species, let alone variations between different species, confuse the picture still more.

The following biochemical data, therefore, are presented with many reservations. Many gaps and omissions are due to the paucity of experiments. Animal experiments are mentioned where those on man are not available. Unfortunately, these must suffice until further experiments are completed.

Chemical and Physical Basis of Proposed Mechanisms of Narcosis

THEORIES OF NARCOSIS

THE TERM NARCOSIS has various meanings. It may be used in a precise, biological sense to designate a depression of activity of protoplasm. When used in such a manner it refers to a depression of all types of cells. It may be used in a clinical sense to designate depression of neuronal activity characterized by deep hypnosis or anesthesia. In this discussion the term is used in a general sense and refers to depression in all types of cells. The terms narcotic and anesthetic, likewise, have both general or specific meanings. In this discussion the terms anesthetic and narcotic refer to agents which suppress activity of all types of cells. Besides the property of affecting all types of cells, anesthetics and narcotics have a special predilection for nervous tissues. The essential difference between narcotic and non-narcotic depressants is that the effects of narcotics are reversible and the cells revert to normal when the offending substance is removed. Substances which depress the central nervous system are classed pharmacologically as *anesthetics, narcotics, hypnotics* or *sedatives*. These are pharmacological terms used to describe clinical phenomena and do not, therefore, enter into this discussion.

Ever since anesthesia was discovered investigators have been attempting to determine how narcosis comes about. Considerable data has accumulated in support of a number of theories but the exact mechanism causing narcosis remains to be determined. The fact that so many chemically dissimlar substances appear to produce the same physiological end result has led to the perusal of what is often called the *unitarian concept of narcosis*. The numerous investigators interested in this phase of biological change have been unable to ascribe narcosis to any one particular mechanism. Perhaps more than one mechanism causes the change. Since our knowledge remains speculative and inconclusive, the mechanism proposed by individual workers are known as the *theories of narcosis*. Many of the theories have been disproved and are, therefore, obsolete. A discussion of most of the theories is largely of historical interest. Nonetheless many of the workers, while attempting to obtain proof, have made basic observations which are not only of academic interest but have also some practical application. They, therefore, merit discussion on this basis alone, if for no other reason.

The theories of narcosis are not easily classified due to overlapping of ideas and encroachment of one theory into another. Usually they are classed according to the underlying physical or chemi-

cal theme, as for example, "the change in permeability theory," "the adsorption theory," "colloid theory," "lipoid solubility theory," etc. Most theories fall into one of four broad general classifications as follows:

(1) Theories based on solubility. These postulate that the effects of a drug are due to a specific solubility it possesses *in certain cellular constituents.* These theories are concerned chiefly with high solubility in intracellular lipoids or poor solubility in water. Most anesthetic drugs have a high lipoid solubility.

(2) Theories based upon physiochemical changes in the components of protoplasm. Modifications of the colloidal state of the cells, changes in surface tension, adsorption of the narcotic to the cell membrane or on the intracellular colloidal surfaces, changes in viscosity, dehydration of the cell are alleged to caused alteration of normal behavior.

(3) Theories which ascribe narcosis to diminished oxidation in the cell. Decreased oxidation is alleged to come *about either by depriving the cell of* oxygen, by modifying the ability of the cells to use oxygen, or preventing the utilization of the energy which could be released by oxidation.

(4) Theories based upon physical changes in cells, such as reversal of electrical polarity of cerebral cells or decreased electrical activity of cells.

LIPOID AND WATER SOLUBILITY AND ANESTHESIA

The fact that anesthetics are *lipophilic,* that is, highly soluble in lipoids, has

been known for some time. Several early workers ascribed narcosis to solubility of the anesthetic drug in *lipoid* or fatty substances. Bibra and Harless (1847) noted that ether, ethyl chloride, and acetic ether[*] were highly soluble in lipoids and suggested that anesthetic drugs dissolved the lipoid from the brain cells and caused this lipoid to be deposited in the liver. They analyzed the concentration of lipoids in brain and liver before and after anesthesia and found an increase in the liver and a decrease in brain. The reversibility of anesthetics was not explained by these workers. Hermann (1866) stated that narcosis was a result of direct action of the drug on the intracellular lipoids for which the drug has a special affinity. These workers felt sterols and lecithins were the lipoids specifically involved. Exactly how they produced their effect once in the cell they were unable to say. Riecher (1908) demonstrated an increase in blood lipoids during chloroform anesthesia and attributed narcosis to solution of the lipoid from the cell by the drug. Pohl (1891) showed that erythrocytes absorbed and carried more chloroform than plasma. He assumed this to be due to the presence of the lipoids in the cell which absorbed it. He likewise found more chloroform in brain than other tissues. Richet showed that as water solubility decreased, potency of many drugs increased. This is the converse of the lipoid theory. There are, however, too many exceptions to this generalization of potency and decreasing water solubility which make this theory untenable.

OVERTON-MEYER THEORY

Overton (1899) and Meyer (1901) observed independently that the potency

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[*] Ethyl acetate.

of narcotic drugs bears a strong relationship to their comparative solubility in water and lipoids. Inasmuch as these workers arrived at the same conclusions independently and at approximately the same time, their theory bears both their names and is called the *Overton-Meyer Theory*. The Overton-Meyer Theory gained wide acceptance and continues to be referred to by students of the problem of narcosis, even though it is admitted that it does not explain the phenomenon of narcosis. The essence of their observations may be stated as follows: *Chemically inert* substances which are not quickly destroyed or eliminated by the cell are absorbed preferentially by cells in which lipoids predominate. These substances are, relatively speaking, poorly soluble in water but they may be sufficiently soluble to permit transport to the cells. This water solubility is ordinarily less than that in lipoids.

The ratio of the solubility, expressed in moles per given quantity of lipoids, to that in an equal volume of water is called the *oil/water ratio*. Theoretically, as well as practically, the higher the numerical value of this ratio, the greater is the narcotic potency of the substance. Chloroform, for example, has a ratio of 100 while halothane, which is more potent, has a ratio of 330. However, there are exceptions to this generalization. Methane, for example, has a high lipoid, low water solubility and, therefore, a high coefficient. However, it is ineffective as an anesthetic. Saturated hydrocarbons are less soluble in water than unsaturated. This may account for their biological inertness since the drug is unable to reach the cells in ample quantities.

Overton and Meyer also noted that the minimum quantity of a substance necessary for narcosis (which they designated as the *minimal value*) increased as the numerical value of the ratio decreased. In other words, the smaller the ratio, the less potent the drug and the greater the concentration necessary for narcosis.

Meyer obtained his distribution coefficients by dissolving a known quantity of a drug in olive oil, shaking the mixture with an equal volume of water, and determining the partition of the drug between the oil and water, after allowing each layer to separate. The less soluble in water and the more miscible with lipoids a substance is the greater the amount in the oily layer and the higher the ratio. Overton examined a large series of substances. In some cases he determined their ratios experimentally, while in others he calculated the ratio from the solubility of the substance in water and oil.

K. Meyer, in collaboration with others, determined the solubility of vapors of various volatile anesthetics in oil. In addition he determined the concentration necessary for narcosis in frogs and mice. He calculated the concentration of drug in the lipoid in moles per liter from this data. He found that the concentration in lipoids *in moles per liter* was a constant value. This constancy of molecular concentration is an experimental fact of importance which will be alluded to later in discussion of other theories of narcosis. In other words, the *molar* concentration of a chemically indifferent substance required for narcosis, even though it varies in potency, is a fixed value. Meyer showed also that the concentration of the narcotic depends upon the type of cell affected rather than on the nature of the drug. One can see from Table I.27 taken from Meyer, that the concentration is nearly constant and averages 0.06 moles per liter. The lipoids of

TABLE I.27

THE RELATIONSHIP OF THE DISTRIBUTION OF
VARIOUS ANESTHETICS BETWEEN OIL AND
WATER, THEIR ANESTHETIC CONCEN-
TRATION AND THE AMOUNT
IN THE BRAIN

	Vapor per 100 cc. oil	Volumes % of Anesthetic	Moles per Liter Conc. in Brain Lipoid
Methane	0.54	37.0	.08
Ethylene	1.3	80.0	.04
Nitrous Oxide	1.4	100.0	.06
Dimethyl Ether	11.6	12.0	.06
Acetylene	11.8	65.0	.05
Methyl Chloride	40.5	6.5	.07
Ethyl Chloride	40.5	5.0	.08
Ether	50.0	3.4	.07
Amylene	65.0	4.0	.10
Chloroform	265.0	0.5	.05

the cell are believed, by Meyer, to be alcoholic in nature (sterols). Studies of the interrelationship of lipoids and anesthetics have emphasized principally the affinity of the cell for the anesthetic drug. They in no way take into account or explain the problem of alterations in cell membranes through which these substances must pass or what happens in the cell once the drug passes inward.

There are a number of objections to the Overton-Meyer Theory. One objection is that the data represents in vitro studies in olive, seasame and other vegetable oils. Animal oils were not used. Another objection is that the solubility has been determined in pure water. The solubility of the drug in pure water differs from the solubility in lymph. Another objection is that most of the experiments of early investigators were performed at room temperature (20°C.). The mammalian body temperature is 37.5°C. Discrepancies naturally appear between data obtained at 20° and at 37.5°C. *because of the difference in solubility due to temperature.* The solubility may increase or decrease as temperature changes. The narcotic effect rises and falls in a parallel manner with solubility. Also water is a peculiar solvent which can be influenced by hydrogen bonding and thus cause discrepancies which cause individual compounds to fall out of line.

Clinicians often assume that the oil/water ratio is an index of the quantity of an anesthetic absorbed by brain and other nervous tissue. This is not a strictly correct assumption. It is true that nerve tissues are rich in lipoids when compared to other tissues. However, they contain from 75% to 90% water, depending on the area from which the tissue is obtained. Less than 50% of the solids in nerve cells are lipoids. The special predilection anesthetics have for nervous tissue is not wholly due to the lipoid content of the tissue. The total perfusion of the brain by blood, the blood brain barrier and water solubility are factors which must also be considered. Adipose tissues are richer in lipoids than nervous tissues. However, they take up less drug than brain because they are poorly perfused due to a less profuse blood supply. Lipoids vary in their chemical nature and may, therefore, have different affinities and solubilities for narcotics. Tissues which have a relatively low lipoid content, for example muscle (contains approximately 2% lipoid), absorb less anesthetics than brain and nerve, even though they have an abundant blood supply. Ball and Cooper (1949) in studying the activity of phosphorous compounds believe the lipophilic action of narcotics may derange phospholipids serving to approximate and cement to the area of activity the enzymes which function in metabolic cycles.

The Overton-Meyer Theory explains the transport of an anesthetic from and to the cell. It is concerned with potency of narcotics but sheds no light upon the

action the drug exerts once it gains access to the cell.

The Overton-Meyer Theory, when first postulated, explained the behavior of *straight chain* aliphatic compounds. It was not applicable to aromatic compounds and heterocyclic compounds. Numerous aromatic substances have high lipoid distribution coefficients but manifest no narcotic potency. The theory has recently been extended to other inert substances. Recent studies on the anesthetic qualities of inert gases, such as xenon, argon, nitrogen (under pressure) reveal that the theory also applies to these substances. These gases possess relatively high degrees of lipoid solubility and behave like the inert aliphatic compounds.

REACTIVE COMPOUNDS AND LIPOID SOLUBILITY

Lipoid solubility is not confined to inert substances. Many chemically active substances manifest varying degrees of attraction for lipoids. Barbiturates, local anesthetics, opiates, ureides and other reactive molecules are also lipoid soluble. They, however, do not fit into the Meyer-Overton scheme because they are polar substances. Local anesthetics, for example, have two polar groups; one a hydrocarbon which is lipophilic and one an amino group which is hydrophilic. The amino group becomes oriented into the aqueous phase of the axone-lymph preparation. The hydrocarbon nucleus orients into the lipoid of the axone. Local anesthetics are metabolized also. Since they are polar and reactive they can hardly follow the Meyer-Overton Rule.

In spite of the fact that the lipoid theory is beset with objections and is invalid, it is constantly being alluded to in discussion on narcosis and related bio-

logical phenomenon. More recently the approach in the study of narcosis by Ferguson, Brink, Pasternak, Featherstone and Wulf and others has been to look more closely at the atom and molecule itself and to study its behavior in relation to the cell. This has again involved the question of solubility of narcotics. These ideas will be elaborated upon further in this chapter.

COLLOIDAL CHANGES IN ANESTHESIA

COLLOIDS AND PROTOPLASM

The effect of narcotics on the physiochemical behavior of colloids has been studied in vitro and to some extent in vivo. Artificial cell models, composed of colloidal solutions surrounded by semipermeable membranes, have been used extensively in such studies. Such cell models have been studied with varying concentrations of narcotics after inducing changes in viscosity, coagulability, adsorbability, intracellular oxidation, state of hydration and alteration in permeability to ions. These changes together with exposure to narcotics produced a subsequent depression of activity in the cell. In order to provide a background to better understand this aspect of narcosis a discussion of the behavior of colloids related to protoplasm is necessary at this point.

NATURE OF COLLOIDS

The physical basis of protoplasm is colloidal in character. A colloid is a solution of large sized particles dispersed in a solvent. The distinguishing feature between a colloidal solution, a true solution, and suspension is in the size of the particles dispersed in the solvent. In *all solutions* the particles of solute are referred to as the *dispersed phase*. The

solvent is the *dispersion medium*. In a true solution the particles are individual molecules or ions whose diameters are less than one millimicron (1.0 mμ). The smallest particle visible to the eye, aided by the most powerful microscope, has a diameter of approximately 200 millimicrons. Particles in a true and colloidal solution therefore are not visible. In other than true solutions the particles of solute are composed of excessively large molecules or as aggregates of smaller ones. When these aggregates are less than 200 millimicrons in diameter, the solution is termed a *colloid;* when they are greater the solution is termed a *suspension*. Colloidal solutions are subdivided into *suspensoids* and *emulsoids*.

Suspensoids are often called *lyophobic* colloids because the particles have little or no affinity for the solvent. The term *lyophobic* actually means "fear of water." Solutions composed of molecular aggregates of finely divided metals, such as colloidal gold or silver are placed into this category. The particles of a lyophobic suspensoid carry a well defined electrical charge which tends to keep them separated and suspended. A change in the *sign of the electrical charge or an increase in molecular activity*, as would result if a solution were heated, brings the particles *closer together*. They then clump into larger sized particles. In this state they may be too large to remain suspended and precipitate out of solution. Suspensoids are easily precipitated if electrolytes which cause changes in electrical charges are added to the solution. Precipitation of a suspensoid is not reversible.

HYDROPHILIC AND HYDROPHOBIC PROPERTIES

Emulsoids are called *hydrophilic* or

lyophilic colloids because the particles in the solution have great affinity for the solvent. The terms lyophilic and hydrophilic mean attraction for water. Emulsoids are important biologically because they abound in protoplasm. They are the solutions comprising the proteins, lipoids and high molecular weight carbohydrates in the cells. The viscosity of an *emulsoid* is noticeably greater than that of the dispersion medium from which it is composed. On the other hand the viscosity of a *suspensoid* differs only slightly from that of the solvent. The particles in an emulsoid, like those of a suspensoid, may aggregate into larger sized particles and flocculate (or precipitate) out of solution. However, they may be restored into their colloidal state by changing the reaction of the solvent. The precipitation of an emulsoid, therefore, unlike that of a suspensoid, may be reversible. The charges on the particles of an emulsoid may be neutralized so that the solution is isoelectric. By this is meant that the molecules of the dispersion medium are at the point of electrical neutrality. The particles of an emulsoid are hydrophilic and readily take on water. If the particles remain hydrated the *colloid* is stable. Dehydrating agents (alcohol and salts) cause precipitation of an emulsoid by *removing water*. The reversal of precipitation is called *peptization*. In some colloidal systems, electrolytes or other colloids are added to prevent aggregation. These, referred to as *peptizing agents*, act by stabilizing the electrical charge on the surface or by providing a protective film around the particle.

PHYSICAL BEHAVIOR OF COLLOIDAL SOLUTIONS

Colloidal solutions contain, numerically speaking, a small number of particles.

The particles, however, may be very large relative to those found in true solutions. The physiochemical properties of a colloidal solution are not dependent upon the chemical nature of the particles, but, rather, upon the total number of particles. Therefore, colloidal solutions exhibit negligible osmotic pressure (see Chap. 1). The vapor pressure, the freezing and boiling points of colloidal solutions are nearly the same as those of the solvent.

Colloidal solutions manifest a phenomenon known as the *Tyndall* effect. This is produced by passing a concentrated beam of light through the solution and viewing the beam at right angles. A whitish turbidity is observed which is due to the reflection of light from the particles. A true solution does not exhibit this phenomenon because the particles are too small to reflect light. The turbidity, if examined closely under magnification, appears to be due to numerous discrete points of light, each of which is a reflection from an individual particle in the solution. Each point of light appears to be in a continuous violent vibratory motion. This motion is due to the bombardment of the dispersed particles by the molecules of the solvent. This movement is known as the *Brownian movement*. The instrument used to visualize this activity is called the *ultra-microscope*.

ANESTHESIA AND COLLOIDS

The fact that anesthetics affect the colloids in protoplasm was first voiced by Ranke (1867) who observed a clouding of saline extracts of muscle and nerve cells upon the addition of small amounts of chloroform. He also noted that protoplasm of infusoria became darker if chloroform were added to the fluid surrounding the cell. Binz (1877) noted a coagulation of protein in brain cells by dilute chloral or morphine solutions. Claude Bernard (1875) also observed similar phenomena and attributed them to reversible flocculation in the colloids of the cells. He was the first to announce a theory of narcosis based upon flocculation of colloids. He assumed that all anesthetics, though chemically different, acted in a similar manner. He is, therefore, credited with conceiving the unitarian concept of narcosis. The theory that flocculation of colloids causes narcosis is refuted because the studies were in vitro and the concentrations of drugs used were greater than those ordinarily found during narcosis in vivo.

ULTRAMICROSCOPIC CHANGES (BANCROFT)

The theory was abandoned for some time but was revived by Bancroft in 1931. He postulated that narcotics do act by causing flocculation of colloid particles but that this flocculation is microscopic and not macroscopic. A reversal of this flocculation (peptization) causes a return of vital functions. Bancroft studied living yeast cells with an ultra-microscope. He observed the effects of chloroform, ether, chloral hydrate and other drugs upon Brownian movement. Brownian movement decreased and flocculation became apparent during narcosis. Washing the anesthetic from the cell caused peptization and renewed activity. The cells regained their ability to ferment carbohydrates and to multiply. Bancroft also noted an increase in irritability of the cell prior to the depression which accompanied aggregation of the colloid particles. He observed further that thiocyanates antagonized the depression.

HYDRATION OF COLLOIDS

The particles in an emulsoid imbibe water to form a hydrated structure known as a *gel* when subjected to variations in hydrogen ion concentration, temperature and other changes. Gel formation is probably responsible for the physical form of protoplasm. Changes in the colloidal state from any cause, therefore, results in changes in water content and a change in viscosity of the colloid in the cells. Anything which causes flocculation, which is the reverse of gel formation, causes water to be lost from the colloid. Since anesthetics cause flocculation they would cause loss of fluid. *Dehydration* of animal and plant cells exposed to anesthetics has been observed by numerous investigators. It is not surprising then to find that investigators have proposed the loss of water as the cause of depressed cellular activity. Dubois (1882) noted that depressant drugs caused an irreversible transudation of fluid from plant cells. Stephanowski (1902) noted a reversible dehydration by chloroform in vorticella, a unicellular plant. Knaffl-Lenz (1908) noted that alcohol, ether, and other narcotic substances caused a shrinkage in volume of erythrocytes suspended in saline solutions which he felt resulted from loss of water from the cell. Höber (1907) likewise associated shrinkage of cells with water loss and with anesthesia. Kochman (1923) noted that various anesthetic drugs caused a shrinkage in fragments of fibrin. This process was reversible. Dehydration, however, is not necessarily a constant finding in narcosis. Increased activity has also been seen in some cells when fluid was lost. Frog muscle cells, for example, respond with increased irritability if treated with glycerin, which is a dehydrating agent. The dehydration theory like many others lacks adequate proof and has many exceptions.

THIXOTROPY AND ANESTHESIA

The thixotropic setting theory of Siefritz (1941, 1950) likewise falls into the category of colloidal changes. Observations were made on gelation of slime mold when exposed to various anesthetic agents. The term thixotropic is used to indicate a reversible gelatinization of protein. The term refers particularly to certain gels which liquefy when subjected to the action of vibratory forces, such as shaking or ultrasonic waves. Gelation or setting recurs when the liquefied substance is allowed to stand. The addition of electrolytes and other substances causes the gel to re-form. Certain anesthetic agents apparently initiate the same response. This theory is beset with the same objections common to other theories of dehydration and coagulation. The observations were made in non-mammalian tissues. Concentrations of drug employed were far above those used clinically. The phenomenon of tachyphylaxis was observed with commonly employed agents (cyclopropane, ethyl chloride) which do not manifest it ordinarily during clinical anesthesia.

SURFACE PHENOMENON AND ANESTHESIA

The total surface area of the particles in a colloid solution is immense. The more particles into which a given volume of a substance is subdivided the greater is the surface presented by that mass to a dispersion medium in which it is suspended. In a colloidal solution a small quantity of a substance is subdivided into many small aggregates. These present a large surface to the dispersion medium and thereby create an

immense interphase. Consequently, surface phenomenon which come into play at the interphases formed between the solute and solvent in colloidal systems assume considerable importance.

ADSORPTION AND ANESTHESIA

NATURE OF ADSORPTION

Certain substances tend to become concentrated on the surface of a solid or liquid by a process called *adsorption*. Adsorption is a type of adhesion which takes place when a substance in a medium is in contact with another medium. An increased concentration of molecules occurs from that medium on the surface of the newly added medium. Adsorption is a physical process rather than a chemical union. Charcoal, silica gel and colloidal hydroxides, such as those of aluminum possess the attribute of adsorbing chemicals to their surfaces. There are various types of adsorption. The adsorption is said to be polar when the material adsorbed (adsorbate) consists of positive and negative ions. In this case the adsorbed film has an over-all electrical charge. The term polar adsorption is also applied when adsorption is due to attraction of polar groups in the adsorbate for the adsorbent. The accumulation of the adsorbed substance at the boundary of the adsorbing surfaces and the medium holding them assumes a definite pattern A fatty acid added to an oil/water system becomes distributed over a single layer of molecules over the interphase. The carboxyl group of the acid is oriented into the water since it is chemically similar to this substance. The alkyl portion of the molecule (hydrocarbon residue) is oriented into the oil with which it is chemically allied. The carboxyl group is called a "polar" group, the alkyl residue

the "non-polar" group. Thus, droplets of lipid in water could adsorb a fatty acid without combining with it. On the basis of the mechanisms involved adsorption may be classed as chemical (chemosorption) or Van der Waals adsorption. In chemosorption forces of a chemical (valence) nature are involved. In Van der Waals adsorption the electrical forces exhibited by non-polar molecules of the non-valence type are involved. Heat exchange is involved in adsorption. In the Van der Waals type heats of adsorption are of low magnitude. The heat changes are of the same order of magnitude as the heats of vaporization (5 to 10 kilocalories per mole). Chemosorption involves larger quantities of heat. It is observed at higher temperatures.

Adsorption may be specific. By this is meant that one substance is adsorbed preferentially over others. Adsorption may be directional in which case the adsorbed molecules are directionally arranged on the adsorbed surface. Adsorption may be negative in which case the concentration of adsorbate is less on the surface than in the surrounding medium. A surface of an adsorbent may be activated by heating and driving off molecules of adsorbate.

The degree of adsorption varies with changes in temperature. It decreases as the temperature increases and increases as the temperature is reduced. Gases which ordinarily are not adsorbed by activated charcoal at room temperature maybe removed from a mixture by adsorption by extreme cooling. The amount of substance adsorbed by a unit mass of adsorbent varies with the concentration in the solution, the nature of the adsorbent, and the temperature of the medium. The amount adsorbed is a constant value for a given substance, at a

given set of experimental conditions. Thus, an adsorption equilibrium is established for a particular substance at a given temperature and concentration. The amount adsorbed is not necessarily in direct proportion to the concentration. Adsorption is relatively greater in dilute solutions. The curve obtained by plotting concentrations against the amount adsorbed when conditions are isothermal is called the *adsorption isotherm*. Equations expressing the relationships of adsorption have been proposed by numerous workers. The classical one is that of Freundlich. Langmuir also proposed one. Both Freundlich's and Langmuir's are applicable to gases. The degree of adsorption is usually studied by plotting the adsorption isotherm, or determining the decrease in concentration of the substance in the dispersion medium when various quantities of absorbent and agent are mixed.

ADSORPTION AND ANESTHESIA

Some narcotics are readily adsorbed to activated surfaces. Barbiturates and local anesthetics, for example, are readily adsorbed by activated charcoal added to dilute aqueous solutions. This ready adsorbability of depressants has been the basis of one of the theories of narcosis. King (1930) and others noted a parallelism between narcotic activity and the quantity of various narcotics adsorbed at a paraffin-water interface. Lillie and Warburg obtained similar evidence from experiments on plants and animal cells. Hiller observed that certain depressant drugs applied to the surface of amoebae produced narcosis. This response was not obtained when the substance was injected into the cell. Bürger attempted a theoretical explanation of narcosis on the basis of an increased ad-

sorptive capacity of anesthetic drugs resulting from the alleged strain between carbon atoms in the molecules. According to the Bayer-Theile theory of partial valences a strain exists between carbon atoms. This strain is greater in unsaturated substances than saturated and greater in cyclic compounds than straight chain. Saturated hydrocarbons are less potent than unsaturated cyclic hydrocarbons and are, therefore, more potent than straight chain derivatives. Cyclopropane, because of its configuration, allegedly should show a greater strain between its carbon atoms than propylene and, therefore, should be more easily adsorbed. As is the case with other theories the adsorption theory is beset with many exceptions and gaps.

SURFACE AND INTERFACIAL TENSIONS AND ANESTHESIA

Another phenomenon which occurs at liquid interfaces which is of biological interest is that known as *surface tension*. The cohesive forces between molecules of a mass of a substance is not uniform. The molecules in the interior of the mass are acted upon equally in all directions by contiguous molecules. Those on the periphery are acted upon with a greater force by the more numerous molecules in the interior. In a fluid the molecules tend to be drawn inward from the periphery. The number of molecules on the surface, therefore, becomes reduced to a minimum. A given volume of a substance tends to assume the smallest area possible. If the volume of the mass of liquid is small, the mass assumes a spherical form. Particles of liquids assume a spherical shape when they fall as a result of this inward pull of the inner molecules.

If an attempt were made to increase

the surface from this minimum obtainable one, work would be necessary to overcome the forces exerted by the molecules in the interior of the mass upon the molecules on the surface. The energy required to extend the surface is referred to as "free energy." A hypothetical force acting in all directions parallel to the surface substituted for this free energy is called *surface tension*. Such a force is expressed in dynes per sq. cm. and the work done is measured in ergs. Pure water has a surface tension of 70 dynes per sq. cm at 25°C. The surface tension of a liquid varies with the temperature and purity of the liquid. The surface tension of water decreases as temperature increases. Certain chemicals, particularly substances possessing long carbon chains to which are attached carboxyl, hydroxyl and other polar groups (oils, soaps) lower surface tension. In other words, they decrease the attraction between the interior and outer molecules of a drop of water.

Surface tension is a phenomenon occurring at an interface of two dissimilar immiscible liquids. Because this is so, surface tension is linked with and related to adsorption. A substance which reduces the surface tension of another substance accumulates on the surface layer of that substance. In other words, it is readily adsorbed to the surface. The surface tension and adsorption concepts have much in common.

The boundary between a liquid in contact with a gas is known as a *gas-liquid interphase*. An interface also forms when two immiscible liquids are mixed at the boundary of the particles of each liquid. In biological systems interfaces are formed between two immiscible liquids rather than a gas and a liquid. There is some difference between the two types of systems. The behavior of the surface at the liquid-liquid interface is the same as if each liquid were in contact with a gas; namely, there is a contraction of the surface of the mass of liquid. This behavior, as in the case of a liquid in a gas, likewise, results in a greater attraction of the molecules in the interior of the liquid for those at the surface. A free energy, therefore, in such a system. In this case, however, the force is referred to as the *interfacial tension* and not as surface tension. The molecules of one liquid attract the molecules of the other liquid and cause a decrease in the inward pull of the interior molecules on those at the interface. The interfacial tension of a liquid is less than the surface tension of the same liquid in a gas liquid interphase. Two liquids become miscible when the interfacial tension of each becomes zero. Gibbs has demonstrated that adsorption of a substance at an interface is accompanied by a lowering of surface tension.

The fact that surface tension could play a role in narcosis occurred to Traube. He observed, in studies on osmosis, that substances which decreased surface tension passed into cells with greater ease than those which did not. Traube noted a parallelism between the narcotic potency of members of a homologous series of narcotic substances and their ability to lower surface tension in vitro. He studied the surface tension lowering effect of a series of aliphatic straight chain alcohols upon water at 15°C. by measuring their capillary activity. Substances with high degrees of surface tension activity are readily drawn in to capillary tubes. Each member of the series was three times more effective in reducing surface tension than the member which preceded it. A comparison of

the capillary activity at 18°C. of the acetate esters of the following alcohols illustrates this point:

Methyl	58.1 mm.	(1 N)
Ethyl	58.0 mm.	(1/3 N)
Propyl	57.0 mm.	(1/9 N)

However, Traube's theory is untenable for a number of reasons: First, Traube's experiments were done using air-liquid interfaces. Second, too many substances which are potent narcotics are without effect on surface tension. Joachim Ogler (1921) pointed out that many halogenated hydrocarbons which manifest little capillary activity, among them ethyl chloride and chloroform, are potent narcotics. Third, surface tension decreases as body temperature is approached. Traube's observations were made at room temperature. Frank Meyer demonstrated that numerous non-lipoid soluble substances capable of lowering surface tension have no narcotic activity. Trauble (1924) modified his views after further experimentation with absorption of anesthetics by gels containing lipoids and admitted that some mechanism other than capillary activity is involved in narcosis. Recently Featherstone and Wulf have indicated that Traube's data is additional experimental proof of correlation of anesthetic properties with Van der Waals' forces. This is discussed further on.

PERMEABILITY OF THE CELL
MEMBRANE AND ANESTHESIA

The living cell is surrounded by a film or membrane which delineates the protoplasm from its environment. This membrane permits passage of water, electrolytes, metabolites and other substances into and out of the cell by a process of *selective permeability*. In most living cells no actual membrane is demon-

strable histologically or can be separated from the rest of the cell. There has been much speculation in the past concerning the makeup of the membrane. The membrane was believed by early workers to be a film at the surface composed of a layer of the same constituents present within the cell but at increased concentration. The mechanism causing the increase in concentration was believed to be similar to that which occurs when the suface tension of a solvent is lowered by a solute. The constituents ordinarily found in the cell membrane were thought to markedly lower surface tension. Other workers proposed that the lipoid substances present in the protoplasm became concentrated in the cell membrane and that they were capable of lowering surface tension. Overton supported the view that the cell membrane was a film composed essentially of lipoids. If this were the case lipoid-soluble substances would be permeable to the membrane. Others proposed that the cell membrane was a complex colloidal emulsion of watery solutions of protein and a lipoidal dispersion. When the cell was at rest, the lipoid was dispersed in the protein solution. The latter was referred to as the *continuous phase*. The addition of certain ions, particularly polyvalent anions, such as those of calcium and aluminum, to such an emulsion caused a reversal of the phase. The system was then converted into one in which the aqueous protein solution became the *dispersed* phase in the lipoid. The lipoid then became the continuous phase. When the continuous phase was water the dissolved protein and the membrane was permeable only to substances soluble in water. When the continuous phase was lipoid, lipophilic substances penetrated into the system. Thus, a re-

versal of the nature of the emulsion in the membrane was believed to result when electrolytes and other agents came into contact with the membrane. These changes in turn caused changes in permeability. These speculations served to explain the phenomenon observed in studies on permeability. They were the forerunners of the present day concept which regards the cell membrane as a film of protein and lipoid material. The protein forms a double layer between which is the lipoid layer in a sandwich-like fashion. The protein molecules are arranged tangentally to the circumference of the cell boundary while the lipoid molecules are arranged at right angles like the spokes on a wheel with possibly some intermeshing with the protein. The hydrophilic groupings on the protein molecule, such as the $(NH_2, CONH)$ etc. become oriented into the water phase both at the exterior and the interior of the cell, while the lipophilic groupings on the protein molecule orient into the centrally located lipoid. The protein molecules have a helicoid (spiral shape), from which various groups, both hydrophilic and hydrophobic, project. It has been postulated that there are vulnerable sections in the protein molecule and that the lipoid, may at various points, approach the cell surface. Molecules foreign to the cell, thus, have not only the protein and lipoid barriers to traverse, but in addition are beset with the possibility of combining with elements in the cell membrane. They may also alter the physical or chemical structure of the constituents of the membrane. They may cause the protein to fold which results in changes in volume of the spiral. If the chemical nature of the cell membrane is such that it absorbs some of the molecules of solute or if it can combine with the solute it may impede progress of a

foreign molecule. If the constituents of the membrane carry polar groups for which the solute molecules have an affinity, passage may likewise also be impeded. Such impedance is referred to as a decrease of permeability.

Much of the data concerning the ability of substances to traverse the cell membrane has been obtained from plant cells, red blood cells or unicellular organisms. Data on human cells are meagre. The concept that anesthetics alter the permeability of the cell membrane and causes narcosis has been proposed by numerous workers. Hober (1907) was the first to advocate the theory. He emphasized the importance of lipoid material in the cell membrane and felt that the drug was adsorbed to the lipoids, thereby decreasing the permeability and causing narcosis. Actually he embodied the lipoid theory with the permeability theory. Stimulating drugs cause not only an increase in permeability but also an increase in irritability. Increase in stability of the membrane is associated with a decrease in permeability and inactivity of the cell. Hober noted that introduction of polar groups, as for example, the carboxyl, hydroxyl and amino, decrease the penetrating capacity of a molecule through a membrane and that non-polar groups (halogens, alkyls) increased the penetrating capacity. Also, in an homologous series the penetration rate rose as the length of the carbon chain increased. In general the following types of chemicals easily traverse the cell membrane. (1) Gases, including the inert as well as the active, (2) highly lipophilic compounds, (3) organic bases (amines but not quaternary compounds), (4) unionized combinations of weak acids and weak bases. Poor penetration is observed with (1) compounds which have low fat solubility

compared to water solubility, (2) salts of organic bases, (3) highly ionized compounds. As a rule, monohydric alcohols, aldehydes, ketones, aliphatic hydrocarbons and their halogenated derivatives and weak organic bases (local anesthetics) pass through readily. Dihydric alcohols and amides of monobasic acids traverse more slowly. Trihydric alcohols, urea and thiourea traverse still more slowly. Tetrahydric alcohols and those with more hydroxyls, sugars, neutral salts of organic acids pass still more slowly.

Although other workers also associated changes in permeability with narcosis, Lillie (1909) was the leading proponent of the theory. He studied the diffusion of carbon dioxide from cells of certain larvae and based changes in permeability upon resulting variations in cell diameter. He observed that a decrease in permeability occurred during narcosis from chloroform, alcohol and other depressants. He noted an increase in size of sea urchin eggs when they were exposed to dilute solution of certain narcotics. He noted that the inward diffusion of ions was decreased during narcosis. Many of his observations were centered about the study of diffusion of intracellular pigments from the interior of the cell. Lillie, likewise, emphasized the importance of lipoids in the cell and observed that their presence or absence exerted considerable influence upon permeability. He felt that the ionic interchange necessary for depolarization and repolarization was retarded because the narcotic decreased the permeability. Winterstein (1915) also observed that narcotics decreased the permeability of cell membranes. His observations were made on permeability of muscle cells to various ions. Winterstein, unlike Lillie, discounted the influence of lipoids. Ostergren has suggested that molecules interact with the lyophilic-protein chains of narcotics and cause the latter to fold and assume a corpuscular shape and thus alter function of the cell. Dode and his associates also suggest that narcotics act upon lipophilic-protein chains of proteins in the cells. McElroy has suggested that penetration of the narcotic into the lipo-protein film of the cell causes an *increase in cell volume and unfolding* and denaturation of the protein which is followed by a decrease in cellular function.

As is the case with other theories the permeability theory is not unitarian and does not explain all situations and has contradictions and exceptions. In some cases permeability is increased during narcosis rather than decreased. A particular drug may increase permeability in one species and decrease it in another and still produce narcosis in each species.

In spite of the evidence against it the theory is difficult to disregard because the concept of permeability change and *variations in physiologic function is well* established in physiology and is constantly being presented. Biological activity *is associated with electrostatic* phenomena known as repolarization and depolarization. In order to have changes in polarity in a cell a change in membrane permeability to certain ions must occur. Depolarization-repolarization phenomena are known to occur at the myoneural membrane, at the axone as the impulses pass down a nerve fibre and other sites. It has been observed that ions penetrate membranes with difficulty. Ions do pass through a membrane, however, but some mechanism of active transport is present which is inherent in the cell membrane to move the ions. Energy is involved in the transfer, since they do not diffuse of their own free will,

but are transported against a gradient. A nerve fibre at rest has an unsymmetrical concentration of ions with a preponderance of potassium on the interior and sodium on the exterior. During activity both ions move freely and depolarization occurs. During restitution sodium ions are extruded outward by a mechanism called the sodium pump (Chap. 21) which becomes active. The sodium pump, which serves to explain the excitation of nerve tissue, is in some ways a restatement of Lillie's idea of permeability. Changes in permeability, however, are probably secondary to more direct action of anesthetics on metabolism. Since energy is required to transport ions across a membrane from an area of lower pressure gradient to a higher one, there is a possibility that narcotics act by causing a decrease in the output of energy. It must be remembered that narcosis can occur both with and without depolarization. Therefore, depolarization cannot be used as a unitarian concept to explain narcosis.

The permeability theory is interesting, however, even though not applicable as an explanation of the cause of narcosis.

VISCOSITY

Interrelated with changes in colloidal behavior and their attendant changes in gelation is the physical property known as *viscosity*. Viscosity (Chap. 2) may be defined as internal friction within a liquid. Viscosity of an aqueous solution decreases as the temperature rises. Solutes which lower the surface tension of water cause an increase in viscosity. The solute becomes concentrated at the surface. This leads to the formation of a viscous layer in a visible film. Ebbecke (1936) suggested that narcotics increased viscosity

and thereby interfered with cellular function by causing an increase in density of the cell membrane. This interferes with diffusion and exchange of substances between the interior of the cell and the extracellular environment as is the case with other theories. There are many exceptions which make this theory untenable. Chloroform and various alcohols, for example, cause viscosity of cytoplasm of animal cells to decrease during narcosis instead of increase. Still they are effective narcotics.

CHEMICAL UNION WITH INTRACELLULAR ELEMENTS

Some theories of narcosis postulated a chemical union between the narcotic and certain cellular constituents. Moore and Roaf (1905) noted that more chloroform was present in the red blood cells than could be accounted for by mere solubility. They noted that a reversible opalescence appeared in the serum during anesthesia and disappeared on recovery. They, therefore, postulated that the drug combined with cellular elements, probably with proteins, since these are more universally present in protoplasm. The combination is a loose one. This resulting compound inhibits the cellular activity thereby causing depression. Chloroform causes no precipitation of proteins when concentrations necessary for anesthesia are present in blood. The concentration required to produce opalescence of the type described by Moore and Roaf is far above that necessary for anesthesia. There is little evidence to support this theory.

OXYGEN CONSUMPTION AND ANESTHESIA

Not long after the importance of intracellular oxidation was established the concept that narcosis could be due to

oxygen deprivation was advanced. Intracellular oxidation was ascribed to the presence in the cell of the bivalent carbon atom by Nef. Matthews-Brown suggested that narcotics inhibit the activity of the carbon atom. Oxygen utilization was decreased and this in turn caused a decrease in cell function. This, of course, had no factual backing. Baglioni likewise suggested that depressant drugs interfered with oxygen utilization. Verworn (1909) likewise advanced an oxygen deprivation theory. He noted that oxygen consumption of cells decreased when they were narcotized. He postulated the narcotic induced changes within the cell which prevented oxygen from diffusing inward. The oxygen was normally stored in protoplasm for metabolic use. He believed that oxygen was utilized by the cell at the same rate in both the pre-narcotized and narcotized phases but that oxygen was unable to pass inward in the narcotized cell. Asphyxia ensued when the oxygen supply was depleted. Evidence to support this supposition was lacking. Anoxia, asphyxia and narcosis are separate and distinct phenomena. The symptoms of anoxia during anesthesia are totally different from those of narcosis. Verworn did not conclusively demonstrate that a decrease in oxygen consumption is the cause of and not the result of narcosis. Barker (1910) ascribed narcosis to the utilization of oxygen by narcotic substances. He noted that during the electrolysis of water less oxygen accumulated at the anode when ether was present in the solution. Mansfield (1909) explained depression by suggesting interference of oxidation by impedance of the passage of oxygen through lipoids by the narcotic. Despite this, the idea that oxidation is inhibited by narcotics has been expressed in different manner by others. Warburg and

Wiesel (1912) observed that oxalic and amino acids adsorbed to activated charcoal became oxidized due to the effect of the charcoal. He noted that the presence of a narcotic inhibited oxidation in such a nonliving physical system. Warburg postulated that molecules of the narcotic were adsorbed in monomolecular layers on the charcoal and prevented adsorption of the acid. He postulated that this carries over to the living cell and that the narcotic blocks the passage of metabolites into the cell. Warburg's concept is unitarian, non-specific and disregards the diverse nature of depressant drugs. The modern concept of polar orientation of molecules at activated surfaces is in conflict with Warburg's ideas. Warburg's ideas laid groundwork for further study on intracellular oxidation, however. Quastel and other workers pursued the thought further and proposed that intracellular oxidation is inhibited by interference of enzymatic activity by the narcotic. The present day concept is that oxygen is transferred to substrates indirectly with various enzyme systems acting as intermediaries. Narcotic substances depress the activity of these intermediaries. In order to facilitate understanding of these concepts, a brief resume of intracellular oxidation is offered at this time.

CELLULAR RESPIRATION
SOURCES OF ENERGY

The energy of living tissues is largely derived from *aerobic oxidation* of organic metabolites. Some energy may also be derived anaerobically, in the absence of oxygen, by the process often referred to as *fermentation*. Muscle cells, for example, may fragment hexose molecules to lactic acid liberating energy in the process. The total energy released from a unit weight of hexose by fermentation is less than that obtained if the

hexose were burned aerobically to carbon dioxide and water.

NATURE OF OXIDATION

Oxidation may be looked upon in one of two ways: (1) It may be the *addition of oxygen* to a compound or (2) the *removal of hydrogen* from it. In either case there is a *loss of electrons* from the substance oxidized. Reduction on the other hand is the reverse of oxidation. It involves the *loss of oxygen* from a compound or the *addition of hydrogen* to it. *Electrons are gained* by the substance reduced. Oxidation and reduction must be considered together because ordinarily when a substance is oxidized the process usually occurs through the agency of another substance which is simultaneously reduced.

RESPIRATORY ENZYMES

Metabolites from which body energy is derived are carbohydrates, fats, or proteins. Oxidation of the metabolites occurs through the medium of enzymes. The cells cannot utilize molecular oxygen directly. These enzymes, called *respiratory enzymes*, either *activate molecular oxygen* so that it easily combines with a given metabolite, known as the substrate, or they *activate hydrogen* atoms on the substrate and facilitate the removal of the hydrogen atoms from the molecule and their transference to other substances which are able to accept or combine with them. Thus, the substrate, sometimes called the *hydrogen donator*, is oxidized and the substance which receives the hydrogen, called the *hydrogen acceptor*, is reduced. Enzymes which facilitate the acceptance of molecular oxygen by a substrate are known as *oxidases*. Enzymes which effect the removal of hydrogen from a substrate are known as *dehydrogenases*. Agents are

present in the tissues which act as intermediates or "come-betweens" the dehydrogenases and oxidases.

Thus three types of oxidative responses may occur in cells. (1) A dehydrogenase may act alone, without the aid of an intermediate carrier, to remove hydrogen and transfer it directly to molecular oxygen to form water. Neither a carrier nor oxidase is required. (2) Oxidases may activate molecular oxygen so that a combination may be effected with the metabolite directly. No carriers or dehydrogenases are required. (3) A dehydrogenase may activate hydrogen which is removed from the substrate and passed on by the aid of one or more intermediate substances to oxygen. The oxygen cannot be utilized directly but must first be activated by an oxidase. The processes is the same as 1 and 2 except that both oxidase and dehyrogenase are involved together with intermediaries.

OXIDATION IN CELLS

The simple, direct processes of addition of oxygen or removal of hydrogen are uncommon in living cells. Most oxidations involve the simultaneous use of the combination of oxidases, dehydrogenases and carriers. Instead of oxygen being combined directly to the substrate, the electrons are passed along from the substrate to several intermediate substances which in turn transfer them to the oxygen to form water. A certain pigment known as *cytochrome*, found in many types of aerobic cells, is capable of accepting electrons. It, therefore, acts as a hydrogen acceptor. The hydrogen is converted to hydrogen ion which remains in solution. Three types of cytochrome have been identified in tissues (a, b, and c). Each is quite similar to the other and all resemble *hemochromogens*

in structure. They contain iron in the ferrous state. This iron is oxidized to the ferric state by molecular oxygen. The conversion of iron from the ferrous to the ferric state, in a sense, makes iron an oxygen carrier. Cytochrome may be oxidized by a specific oxidase known as the *respiratory enzyme of Warburg*. Two electrons are accepted by oxygen from cytochrome which, with H^+ present in solution, forms water. Cytochrome c is auto-oxidizable. By this is meant that no oxidase is required for oxidation but that the enzyme combines directly with molecular oxygen. Some dehydrogenases transfer hydrogen directly from the substrate to cytochrome. Succino-dehydrogenase of muscle activates hydrogen and transfers it directly to cytochrome. However, the majority of the oxidations require one or more intermediate hydrogen carriers. Hydrogen carriers are capable of alternately becoming oxidized and reduced and, thus, bring about oxidation in steps. As many as three carriers may be involved in an *oxidation-reduction system*.

One of the important hydrogen carriers is *phosphopyridine nucleotide*. This is a complex substance formed from adenine, nicotine amide, di-ribose and phosphoric acid combined with a protein. Two nucleotides of this type have been identified—a *di*phosphopyridine nucleotide and a *tri*phosphopyridine nucleotide. These are usually referred to as coenzyme I and II, respectively. Another carrier of importance of somewhat similar type is the *yellow enzyme of Warburg*. This consists of flavin, a nucleotide, and protein. This is called flavin monophosphate (F.M.N.). These have been known for quite sometime. Recently other hydrogen transfer coenzymes have been discovered. Another flavoprotein known as flavin adenine dinucleotide (F.A.D.) mediates the first step of oxidation of the lower fatty acids. Lipoic acid (6,8 dithiolactanoic acid) likewise has been recently found to participate in hydrogen transfer. More recently still, a new quinone, coenzyme Q, has been isolated. This is found in the lipoprotein in the mitachondria and appears to function in a non-aqueous medium. Apparently the lipoids in the mitachondria exist as isolated areas or islets in an aqueous sea and this enzyme is found in these goblets.

In addition to the cytochromes four carbon dicarboxylic acids, malic, succinic, fumaric and oxaloacetic, are capable of being alternately reduced and oxidized so that they act as both hydrogen acceptors and donators since they can be converted from one to the other. *Ascorbic acid* is also capable of being oxidized and reduced and, therefore, acts as a carrier. Glutathione and a number of diphenols act similarly. It is interesting to note that a number of vitamins play important roles in oxidation-reduction systems. Among these are *nicotinic acid* (found in the coenzymes), *thiamine, riboflavin* and ascorbic acid. Thiamine pyrophosphate (cocarboxylase) facilitates the oxidation of pyruvic acid to carbon dioxide and water. The train of events involved in the use of coenzymes in oxidation is as follows: The substrate is activated by a dehydrogenase which facilitates the transference of hydrogen to the pyridine nucleotide. The nucleotide accepts the hydrogen and is thereby reduced while the substrate becomes oxidized. The pyridine nucleotide in turn is oxidized by passing electrons to a second hydrogen acceptor, possibly to one of the flavoprotein system. This, in turn, transfers electrons to each of the cytochromes successively. The cytochromes are oxidized through the action of the

oxidases and oxygen to form water and liberate energy.

Molecular oxygen can be utilized directly by the cell only when it is activated by oxidases. A number of oxidases have been isolated from plant and animal cells. The respiratory enzyme of Warburg, which has already been described, is essential for oxidation of cytochrome. It is a derivative of *hematin* and, therefore, contains iron. The iron apparently is responsible for the oxygen uptake. The respiratory enzyme is frequently referred to as *indophenol oxidase* because it also catalyzes the oxidation of phenolic compounds. The respiratory enzyme is also called *cytochrome oxidase because* it is involved in the oxidation of cytochrome. A second oxidase which has been isolated is *polyphenol oxidase*. This is so named because it oxidizes various phenols. A third oxidase isolated from living cells is called *monophenol oxidase*. This is believed to be identical with tryosinase. *Tryosinase* also oxidizes phenols. Oxidases act only in aerobic systems, that is, in environments in which oxygen is always available. In certain isolated instances, oxygen may act as a hydrogen acceptor. In this case the system is called an *aerobic dehydrase system*. Oxygen combines with hydrogen to form hydrogen peroxide. Hydrogen peroxide is toxic to tissues. Therefore, an enzyme known as *catalase* is present in tissues which favors the breakdown of the peroxide to water and molecular oxygen. Hydrogen peroxide, therefore, cannot accumulate in tissues in the presence of catalase. Besides catalase, another enzyme is present in tissues which acts on peroxides, called *peroxidase*. Peroxidase decomposes hydrogen peroxide to oxygen and water. It allows utilization of the liberated oxygen since it is a more active oxidizing substance than

ordinary oxygen. Peroxidase and catalase are also pigment type substances derived from hematin and, therefore, contain iron. Iron containing enzymes are poisoned by cyanides.

Many respiratory enzymes exist and have been described. These, as is the case with most enzymes, are specific and catalyze one type of reaction. Lactic dehydrogenase, for example, oxidizes lactic acid to pyruvic acid; succinic dehydrogenase oxidizes succinic acid to fumaric acid while xanthine dehydrogenase (called xanthine oxidase) oxidizes xanthine to uric acid.

Oxidation in most cells may follow one or more of several different paths. Exactly which one of these is utilized is difficult to say. Most probably several types of reactions can occur in a given cell simultaneously.

MICROSPIROMETRY

Tissue respiration is studied by means of a *microspirometer*. Freshly excised, sliced or minced tissues are suspended in saline and incubated at body temperature in the presence of oxygen. The substrate which the cell utilizes as a source of energy, such as lactic acid or glucose, is added. The oxygen is measured by noting the shrinkage in volume by means of a microburette. The oxygen consumption of fresh tissue is expressed as Qo_2. This is defined as the number of cubic milliliters of oxygen per milligram of tissue (dry weight) consumed per hour. The RQ may likewise be determined. Carbon dioxide is absorbed chemically and determined gravimetrically. The microspirometer is generally referred to as the *Warburg apparatus*. Chemical agents added to this incubating cell suspension may either inhibit or increase cellular metabolism. This increase or decrease may be determined

by noting the changes in oxygen consumption and carbon dioxide output. Tissue respiration is inhibited by a variety of chemical substances.

Cyanides, nitrates, and sulphides produce an immediate cessation of respiratory activity. The inactivation is probably due to the combination of these substances with the iron in oxidase since the latter are hematin derivatives.

ANESTHESIA AND TISSUE RESPIRATION

Studies of the respiratory activity of sliced or minced cerebral cortex have yielded widely, varying and in many cases diametrically opposite conclusions concerning the absence, presence or degree of inhibition caused by narcotics and anesthetics. Quastel and his associates were pioneers in studying the effects of narcotics upon tissue respiration in vitro. These workers postulated that narcotics blocked the oxidative mechanism of carbohydrates. The influence of various drugs upon the oxidation of glucose, lactic and pyruvic acids by brain tissue was studied. Ether, chloroform, chloral, chloretone, barbital phenobarbital, morphine, somnifen, nitrous oxide, acetylene and hexobarbital (Evipal), in concentrations of 0.0006 M inhibited respiration of guinea pig cortex in a glucose phosphate medium by approximately 10%. The inhibition became more pronounced as the concentration of narcotics increased. Minced and sliced brain cortex behaved alike. The responses were reversible, which suggests that the concentrations of narcotics used do not injure the cells. Reversibility with ether was not easily demonstrated but the general response did not differ from that of other narcotics.

Sodium succinate and p-phenylenediamine, which are readily oxidized by brain normally, were not affected by narcotics. Likewise, glutamic acid, hexosediphosphate, and α-glycerophosphate were not oxidized by narcotics to the same extent as were glucose and pyruvic acid. The experiments of Quastel showed that narcotics do not prevent oxygen from entering the nerve cells. He felt that they interfere with the breakdown of glucose, lactic acid, or pyruvic acid. The response to the narcotics was immediate. Equilibrium was attained within fifteen minutes. Others besides Quastel reported similar results.

The effects of *morphine, thebaine, and codeine* on lactic, citric and glucose dehydrogenases of rat cerebrum with added substrates were studied by Seevers and Shideman. Inhibition with 0.06%, 0.12% and 0.24% *morphine* occurred. Succinic and alcohol dehydrogenases were not affected by these drugs. Muntwyler, Barlow and Zorn studied the effect of a number of barbiturates upon the oxygen uptake of rat liver slices and the anaerobic reduction of methylene blue by these tissues. *Methylene blue acts as a hydrogen acceptor and is reduced to a colorless compound. The oxygen uptake of the tissues without added substrates was inhibited by the sodium salts of amobarbital, phenobarbital, hexobarbital, alurate, and dial in concentrations varying from 0.001% to 0.1%. The anaerobic reduction of methylene blue was inhibited by barbiturates. Other workers have obtained similar results using slices of kidney and diaphragm (muscle).

Narcotics did not inhibit all oxidative processes to the same extent. The oxidations of glucose, lactate and pyruvate were the most sensitive to the effects of depressant drugs. The same concentrations of drug which affect glucose oxidation do not appear to inhibit oxidation of succinate. The anaerobic breakdown of

glucose to lactic acid is not affected by drugs which inhibit the anaerobic oxidation of glucose. The exact point at which narcotics produce their inhibitory activity is not known. It is known with certainty that they do not inhibit the dehydrogenases or the oxidases. The available evidence indicates that the block occurs somewhere along the carrier system which has just been described at a point between the dehydrogenase and cytochrome c. Metabolism of active cells differs from that of resting cells. A cytochrome link appears to operate during active metabolism but not in the resting state of the cell. It has been speculated that the narcotic blocks either a link between cytochrome b and a or it blocks cytochrome b itself. It is also of interest the narcotics (pentobarbital, chloroform) block the oxidation of glucose and not of succinate. Glucose requires cytochrome for completion of the reaction. Succinate does not. Narcotics do not cause an accumulation of reduced coenzyme as they should if they interfered with coenzyme re-oxidation.

The same objections are raised to this theory that have been raised to others; mainly that the depression of the oxidative processes are the result of and not the cause of narcosis. Those who tend to discount the rôle played by narcotics in inhibiting oxidation argue that the majority of anesthetic drugs investigated mobilize carbohydrate. This causes a lowered carbohydrate content in tissues which in turn causes the depressed respiratory rate. The fact that oxygen consumption of brain in vivo is decreased during anesthesia is not uncontestable proof that narcosis is due to inhibition of cellular respiration. Proof that these drugs act by specific enzyme inhibition is likewise lacking. In order to prove that a drug acts by enzyme inhibition

it is necessary to show that the inhibition occurs in the intact animal with a dose no greater than the one which commonly produces the known drug action and that the inhibition of enzyme activity quantitatively accounts for the drug effect. The most recent idea concerning this entire subject is that the neurons are in a constant state of excitation. The anesthetic state nullifies this excitation and the oxygen consumption falls. There is little difference between the oxygen consumption of the resting and the narcotized cell (Chap. 36). Brain slices obviously are not equivalent to intact nervous tissue. A variety of reasons are offered why excised brain tissue differs from intact brain. According to McElwain the most important difference is that in brain slices stimulation of neurones from adjacent nervous tissue has been interrupted. Stimulated brain tissue is more sensitive to drugs than isolated, dormant, tissue. The cells studied in slices are at rest.

OXIDATIVE PHOSPHORYLATION AND ANESTHESIA

Recently attention has shifted from studies of the oxidative mechanisms and has been directed to the effects of narcotics upon mechanisms concerned with the transfer of energy obtained from oxidation of metabolites to agents which carry on cellular function. The cell must have a ready, immediate source of oxygen. The oxidation of carbohydrates and other metabolites occurs at too slow a rate to adequately meet the needs of the cell. This immediate release of energy is accomplished by the breakdown of compounds possessing high energy phosphate bonds, such as *adenosine triphosphate* (A.T.P.), adenosine diphosphate (A.D.P.) and *creatine phosphate*. Before glucose can enter into the series of reactions whereby it is utilized and oxidized

to carbon dioxide and water, it adds phosphate to carbon number 6. This phosphate it obtained from adenosine triphosphate (A.T.P.) which serves as a coenzyme for the combustion of hexose. The immediate release of energy occurs when adenosine triphosphate (A.T.P.) breaks down to adenosine diphosphate (A.D.P.). This compound is comparable to a storage battery which is a ready source of current. In order to always have a readily available source of energy for immediate release the adenosine triphosphate must be promptly resynthesized and stored. In other words the battery must be recharged promptly. This requires energy which is supplied by a second intermediary substance, known as phosphocreatine. Phosphocreatine breaks down to phosphoric acid and creatine. During oxidation two of the phosphate groups are split off successively to form first adenosine diphosphate (A.D.P.) and then adenylic acid respectively. This system serves as a phosphate transfer device. The adenosine triphosphate (A.T.P.) must be regenerated rapidly and continuously to serve as a steady source of phosphate groups. The phosphate ions necessary are donated to it by hydrolysis of carbohydrate intermediates, such as hexose phosphate, acetyl phosphate or phosphocreatine. The phosphate is in turn donated to glucose. These various phosphate compounds are all esters of phosphoric acid. The hydrolysis of the ester yields energy which the cell utilizes. The energy released during hydrolysis may be small or large depending upon the bonding. The difference in the amount of energy liberated on hydrolysis permits classification of these esters into either low energy or high energy phosphate bonded compounds. Each of the two terminal phosphate bonds of A.T.P. liberate 10,000-12,000 calories per mole. Phosphocreatine liberates a similar amount of energy on hydrolysis. It, therefore, possesses high energy phosphate bonds. On the other hand the various hexose phosphates yield only 2,000-3,000 calories per mole. These are classed as low energy phosphate bonded compounds. The release of energy from the high phosphate bonds occurs in the absence of oxygen. One of the products of breakdown of the hexoses is pyruvic acid. This acid is a three carbon structure derived from glucose. A device known as the citric acid cycle (Krebs cycle) completes the combustion of this acid to carbon dioxide and water. The acid first condenses with oxaloacetic and a four carbon acid. This in turn is oxidized in four steps to carbon dioxide and water with the reformation of a molecule of oxaloacetic acid. This is then ready to repeat the cycle. In the course of oxidation one molecule of pyruvic acid is oxidized to carbon dioxide and water, during which time five atoms of oxygen are utilized and 15 molecules of A.T.P. are synthesized from inorganic phosphate and A.D.P. This process of A.T.P. synthesis is known as oxidative phosphorylation. Since it occurs simultaneously in the same molecule with pyruvate oxidation it is called *coupling*. Fatty acids may also be bonded by the citric acid cycle and provide energy. The reaction is initiated through the medium of A.T.P. and coenzyme A. The fatty acid is not oxidized by the mitachondria but is merely sparked by A.T.P. and oxaloacetic acid. The acid is converted to an active form. This active form is converted to acetyl coenzyme A. Therefore, acetylation is involved. Both processes go on in the mitachondria of the brain and liver.

Certain chemicals causes a dissociation of the oxidation and phosphoryla-

tion and inhibit the synthesis of A.T.P. without necessarily inhibiting oxidation of pyruvate. This dissociation is referred to as *uncoupling*. The best known of the uncoupling agents is dinitrophenol. This is not an anesthetic agent. It produces, instead, a state of hypermetabolism. Uncoupling has had the recent attention of those interested in narcosis. A relationship has been shown between anesthetic potency and the capacity to uncouple oxidative phosphorylation. Brodie and Bain have shown that certain barbiturates (thiopental) act as uncouplers of oxidative phosphorylation. In brains from anesthetized animals the concentrations of creatine phosphates were increased while inorganic phosphates were decreased. This indicates that the hydrolysis of organic phosphates does not occur. There appears to be a selective decrease of A.T.P. formation. They noted an increase in oxygen uptake. Chloral, methadone and other drugs, likewise, appear to uncouple. Other workers have found that the uncoupling effect is confined neither to the brain nor to the liver and is not characteristic of barbiturates alone. The effect has been noted in renal and spinal cord mitachondria. Besides, nitrous oxide, morphine and certain more potent barbiturates do not elicit this phenomenon. Another discrepancy is that concentrations of barbiturates which uncouple also depress oxygen consumption. Some barbiturates do not uncouple. Certain convulsant barbiturates (dimethyl butyl, ethyl butyl barbiturate) do uncouple. The anesthetic potency of these drugs in vivo cannot be correlated with the in vitro behavior.

Along the same vein Quastel and his associates have shown that the synthesis of acetyl choline is inhibited by narcotics in vitro. Although the exact role acetyl choline plays in neuronal activity is not known exactly, the fact that it is essential is well established. Acetyl choline is synthesized by the brain during aerobic metabolism of glucose, pyruvate and other substrates. The synthesis of the acetyl group is suppressed along with that of A.T.P. This would explain the action of anesthetics on a unitarian basis were it a tenable theory. To offset this data in vitro is the fact that in vivo the opposite occurs. Acetyl choline and A.T.P. are both increased while oxygen consumption is decreased—in some cases this is as much as 30%.

Thus, it can be seen that there are objections to the uncoupling theories also and the belief that the anesthetic state is due solely to uncoupling cannot be justified with the evidence at hand. One of the most striking facts in studies of enzymatic activity has been the repeated failure to correlate the response of the drug on an enzyme system in vitro with the effect it produces in the living body. The tissue concentrations of barbiturates in vivo are not sufficient to cause uncoupling.

In order to refute this objection and substantiate the oxidation theory it has been suggested that the drug depresses metabolism at small critical brain centers leaving the overall brain metabolism unchanged. This effect on localized individual cells has an impact on the organism as a whole.

THERMODYNAMIC ACTIVITY OF NARCOTICS

The most recent trend in the study of narcosis has been to correlate narcotic activity with the physical properties of the atoms and molecules of the agent involved and to divest their behavior from the influences of unknown variables such

as interaction with body fluids, cellular constituents, transport to the cell, and so on. Ferguson, in studying chemical potentials as indices of toxicity of drugs, has indicated that the various theories of narcosis which have been presented in the past are not independent theories. Instead, the physical properties of narcotics which were measured, such as vapor pressure, solubility, surface tension, oil-water coefficient, adsorbability and so on were actually measures of the tendency of a substance to distribute itself between two phases. It has been indicated by recent workers that data on *narcosis is of more significance when the* concentrations of the drugs administered are expressed in terms of thermodynamics instead of in the conventional terms, such as volumes percent, milligrams per volume and so on. The concentration, instead, is expressed in terms of ratio of partial pressure of the quantity of substance necessary for narcosis (P_v) to the saturated vapor pressure of the pure compound (P_t) at the conditions of the experiment. When an equilibrium exists between two or more phases the chemical potential (activity) should be the same in all phases.

The ratio of the two vapor pressures is equal to the thermodynamic function known as "activity." It is customary to refer thermodynamic activities to an arbitrary standard to which unit activity is assigned. In this discussion the pure liquid is taken as the standard state having unit thermodynamic activity. A fundamental property of thermodynamic activity is that it is equal in all phases of equilibrium. At equilibrium a steady state exists between the two phases. The rate of uptake of narcotic by the tissues is equal to that which leaves them. At this state the thermodynamic activity

will be equal to the ratio of the partial pressure of the narcotic to its saturated vapor pressure. It has been postulated further that when narcosis occurs by chemically inert molecules a constant fraction of a total volume of some nonaqueous phase of a cell is occupied by narcotic molecules. The thermodynamic activity of a narcotic multiplied by the molal volume is a constant. Brink and Pasternak, elaborating upon Ferguson's idea, suggested that the work required in the transfer of a mole of a narcotic from the pure liquid to the cell is the same for all substances.

If the concentrations are expressed in terms of relative saturations of vapor pressure of the substance (P_v/P_t), the range of the values is greatly reduced from those expressed by conventional terms and the numerical factors are closely alike. The relationships of concentration in volumes percent of inert anesthetics versus thermodynamic equivalent are shown in Table II.27.

TABLE II.27

	Vol. % for Anes.	Partial Pressure /Saturated Pressure
Nitrous Oxide	100.0	0.01
Acetylene	65.0	0.01
Methyl Ether	12.0	0.02
Ethyl Chloride	5.0	0.02
Ethyl Ether	3.4	0.03
Ethyl Bromide	1.9	0.02
Chloroform	0.5	0.01
Fluothane	0.9	0.03

MOLECULAR SHAPE AND SIZE AND ANESTHESIA

Wulf and Featherstone also have correlated narcosis with physical properties of atoms and molecules. The suggestion made by Brink and Pasternak that possibly narcotics produce their effects in regions of the cell into which they can

fit just as they fit in the structure of their own pure liquid intrigued them. These workers, therefore, have correlated narcotic potency with spherical, molecular volume as determined from Van der Waals' constants (Table III. 27). All mol-

TABLE III.27

VAN DER WAALS' CONSTANTS AND NARCOTIC POTENCY

$a = \dfrac{(Liters)^2}{(Moles)^2} \times$ atm.		$b = \dfrac{liters}{moles}$
0.0341	Helium	0 2,370
5.464	Water	0.3,047
3.592	Carbon Dioxide	0.4,267
3.782	Nitrous Oxide	0.4,415
4.194	Xenon	0.5,105
4.390	Acetylene	0.5,136
4.471	Ethylene	0.5,714
5.489	Ethane	0.6,380
8.379	Propylene	0.8,272
12.020	Ethyl Alcohol	0.8,407
10.910	Ethyl Chloride	0.8,651
7.775	Sulphur Hexafluoride	0.8,808
15.170	Chloroform	0.10,220
16.960	Trichlorethylene	0 11,280
17.380	Ethyl Ether	0 13,440

ecules exert a weak attraction upon one another known as the *electronic Van der Waals' attraction*. This is the result of mutual interaction of the orbital electrons of one molecule and the protons of the nuclei of other molecules. This attraction is largely, but not completely, nullified by the repulsion of nuclei for nuclei and electrons for electrons, since like charges repel each other. Van der Waals' attraction is significant when the molecules are composed of many atoms and are close to one another. Van der Waals' forces account for the liquefaction and solidification of substances when temperatures are appropriately reduced. The boiling point is an index of the degree of molecular agitation necessary to overcome this attraction and, therefore, an indication of the magnitude of these forces. In order to correct for the non-ideality of a gas Van der Waal introduced the two constants, one of which represents the attraction of the mole-

cules expressed by (A/v^2) and the other $(V - b)$ which represents the volume of the molecules. The constants are also an index of the spheres of influence of the molecule or atom which are responsible for biologic actions in solution. Solubility is measurable by Van der Waals' constants since solubility is dependent upon attraction and repulsion between solute and solvent. The solubilities of a series of gases in a given liquid increase in the order of their ease of liquefaction. The ease of liquefaction can be correlated with Van der Waals' constants. Therefore, narcotic potency should correlate with the constants. Wulf and Featherstone show that the greater the numerical value of the constants, the more potent the narcotic will be. There are discrepancies, however. Sulphur hexafluoride possesses a low "a" constant which these workers attribute to the differences in bonding of the six fluorine atoms. Water and ethyl alcohol likewise are out of line and have a large "a" constant which they attribute to the high potentials these substances show for hydrogen bonding.

Correlation of molecular volume and narcotic potency has been demonstrated from the parachor values suggested by Sugden (1930). Parachor is a physico-chemical constant computed from surface tension of the liquid phase of a substance and its density. The computation is made from the following equation:

$$P = \frac{M \sqrt{y}}{P_L - P_v}$$

in which $P =$ the parachor, $M =$ the molecular weight of the substance, $y =$ surface tension of the substance in liquid form, $P_l =$ density of liquid at the same temperature, $P_v =$ density of the vapor

at same temperature. The parachor of a substance is proportional to its molecular volume.

PAULING'S ICE CRYSTAL THEORY

Linus Pauling recently (1961) has advanced a theory of narcosis based upon hydration of anesthetics by water. Anesthetics have an attraction for water and form hydrates. They thus are capable of stabilizing the formation of ice crystals. He postulates they bring about unconsciousness by causing the formation of micro-ice crystals in the neurons. These reduce electrical conductivity and thereby interfere with the activity of the brain. He postulates that the anesthetic acts in the watery portion of the brain since the brain contains 78% water. He believes that the conversion of approximately 0.1 of 1% of this water into minute crystals is necessary to induce unconsciousness. Water in the liquid form is a conductor of electricity but in crystalline or ice form it is a poor conductor. Hypothermia produces anesthesia by conversion of a part of the cellular water to crystals. When the brain tissue is cooled small hydrate crystals form trapping ions and electrically charged side chains of protein molecules. The formation of these micro-crystals then interfere with electrical activity of the brain and causes unconsciousness. Pauling's theory postulates that the molecules of an anesthetic supposedly fit into the framework crystal structure of water molecules which compose the hydrated micro-crystals and in this way lend stability to these crystals. Anesthetics permit the formation of these ice crystals at body temperature. Formation of these crystals at body temperature causes unconsciousness just as they do in hypothermia. Ice crystals at 0°C. expand and damage the cell. These crystals of water and an anesthetic do not expand, since they are above the temperature at which water freezes. Thus, this theory attempts to explain narcosis on a molecular basis.

Pauling suggests that xenon, which is completely unreactive save for its ability to form a hydrate, acts in this manner. The attraction between the atoms and xenon and the molecules of water in hydrate crystals make xenon hydrate anesthetic. Helium atoms have a very small attraction for other molecules and do not stabilize the formation of ice crystals. Nitrogen does so, but only under pressure.

The hydrate micro-crystals which form in the brain have cavities of different sizes to accommodate anesthetic molecules of different sizes. The smallest chamber in which an anesthetic molecule fits is formed by 20 water molecules, the next larger by 24 and still the next larger by 28. Pauling assumes that if the hydrate micro-crystals form in the brain, all three kinds of chambers are contained by these hydrate molecules and each would accommodate an anesthetic of different molecular size. Mixture of anesthetics would, therefore, be more effective since molecules of different sizes were employed. Pauling feels that the hydrate micro-crystals also form in tissues other than the brain and possibly the function of other tissues may also be altered.

ELECTRICAL PHENOMENA OF CELLS AND NARCOSIS

Aqueous solutions of electrolytes form a vital part of all living organisms. The cell membrane separates the intracellular ions from the extracellular so the concentration on one side differs from

the other. This creates a potential difference between the interior of the cells and their environment. The potential difference usually undergoes a variation during the activity of the cells. The precise role these electrical processes play in the maintenance of life is not known. These electrical potentials, however, indicate biological activity. The response may be additive for each cell in an organ composed of such cells. The rhythmical activity of certain organs is accompanied by the generation of electrical currents which closely parallel the rhythm of biological activity. Outstanding examples are the heart and the brain. Currents are set up in the entire organ which can be gathered, amplified and their magnitude recorded on a moving film.

The phenomenon of electricity has been associated with anesthesia for some time. Beutner in 1913 observed changes in electrical potential resulting from the addition of alcohols in a simple cell composed of phenol interfaced between layers of sodium and potassium chloride. He postulated that a similar effect occurred in vivo. The concentrations of alcohol employed were far greater than those which would ordinarily be used in vivo. This theory has been referred to as the *Beutner Theory.*

Neurophysiological alterations are the result of narcosis and not the cause. Some of these involve electrical activity of the cell. Most important of these is the electrical activity of the brain.

Brain cells show a spontaneous rhythmical activity which in some ways resembles the activity of the heart. However, in the brain multitudes of different cells are involved, and unlike the heart whose cells act in unison and manifest a single basic rhythm, a complex mixture of different rhythms are developing simultaneously. The fluctuations in electrical activity of the brain can be detected by electrodes placed on the scalp and recorded graphically by means of a recording electrometer, known as an *encephalograph.* The record represents the sum of the voltages developed by individual neurons in a particular area of the cerebral cortex. Presumably the rhythms represent fluctuating potentials produced by the dendrites. The current which develops rises from zero potential to its maximum and reverts back to zero. This occurs many times per second. An indicating lever scribes a record, on a moving paper, consisting of undulations or waves called *cycles.* The height of the wave, often called the *amplitude* depends upon the voltage or potential which develops. The number of waves per second, often referred to as *frequency,* varies with different stages of activity. The voltage which develops is of very small magnitude—in the order of 30 to 300 microvolts. A microvolt is a millionth of a volt. The signal, therefore, must be amplified a million or more times before it effectively operates an indicating recording device. The potential varies with the area of the cortex being explored. Two electrodes are necessary to gather the current to obtain a record. Different areas of the cortex may be explored simultaneously by applying pairs of electrodes over selected areas. Each electrode conducts the current generated into an individual circuit. Each individual circuit is referred to as a channel. An electroencephalogram consisting of a single circuit capable of recording the signals from two electrodes is, therefore, called a *single channel* apparatus. More complex devices have as many as twelve channels. A single channel instrument is adequate for

anesthesiology because cortical potentials from the occipital area yield sufficient information for clinical purposes.

Electrodes may also be imbedded into the substance of the brain into various nuclei by trephining the skull. Such type of electroencephalography is referred to as *deep electrode encephalography*. Ordinarily in clinical anesthesia the cortical potentials are studied. The electrodes are applied to the scalp. Two of the active electrodes are placed about 15 cms. apart in the sagittal plane at least 2 cms. lateral to the midline. The anterior electrode is located at the hairline of the forehead.

Normally, three wave patterns are noted, alpha, beta and delta. The alpha rhythm is observed during wakefulness with the eyes closed. These are collected in the occipital areas of the cortex. The frequency is approximately 10 cycles per second with an amplitude of approximately 50 microvolts. The beta rhythm consists of fluctuations of 20 to 50 cycles per second of an amplitude of 5 to 10 millivolts. The delta rhythm consists of cycles of 1 to 5 per second with a voltage varying between 20 to 200 microvolts. The latter is observed in sleep and in *pathologic states during wakefulness*. Changes in the activity of the brain alter the activity of the cortical potentials. Pathological states do likewise. The electroencephalograph amplifies currents of very small magnitude; therefore stray currents and radiation from electrical apparatus, lighting circuits, or high frequency units produce interference and artefacts in records and render the instrument useless.

Cortical potentials are altered by central nervous system depressants. The activity of the brain is suppressed as drug induced depression becomes more pronounced. The suppression is proportional

to the quantity of drug in the brain. The fluctuations in activity during anesthesia are reproducible for given drug in a given patient at a given cerebral cellular concentration. They vary little from person to person for a given drug. The discharge is serial, that is, it is reproductable and disappears and reappears in the same variations in pattern as the concentration is varied. The changes occur very rapidly. Generally the clinical signs of reflex activity lag behind the return or disappearance of cortical activity.

Depressant drugs cause the brain to discharge as a unit instead of from multiple localized areas. Local differences disappear and synchronization of activity of the cortex appears. The rhythm is simplified from the cortical rhythm seen in the conscious subject. Stages of depression may be correlated with blood concentration when depression is due to volatile drugs; the correlation is not as clear when due to non-volatile drugs. The encephalogram is clinically useful for determining depth of anesthesia because the suppression is proportional to the quantity of drug in the brain and that the changes produced are reproducible for a given drug in a given patient without much variations.

Certain basic changes in pattern common to most drugs are observed in the tracing. Usually, as anesthesia is commenced, *there is an increase in frequency* from the pattern seen during consciousness to 20-30 cycles per second (Fig. 1.27). The voltage remains unchanged. After this, small rapid waves appear and gradually these are replaced by larger waves at a slower rhythm, varying from 1-5 cycles per second. The voltage varies anywhere from 5 to 300 μv. per second. As the concentration of the drug in the brain increases, the higher frequency
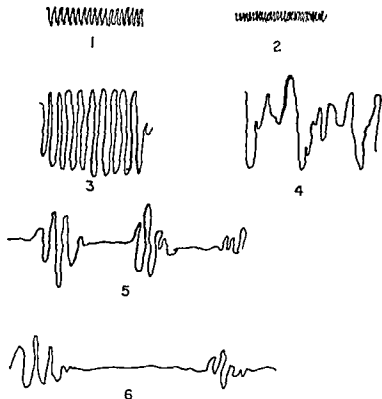
Fig. 1.27. (1) (See text.) Awake pattern 18-13 cps.—50 or less microvolts. (2) Fast frequency—low voltage. Activity of 20-30 cps. (loss of consciousness) and 20 microvolts or less. (3) Slower frequency (4-8 cps.), rhythmical, increased voltage (100-200 u.v.) (light anesthesia). (4) Mixed pattern, low voltage, fast frequency, superimposed on high voltage, low frequency. (5) Periods of inactivity separated by periods of activity of less than 3 seconds. Referred to as burst suppression (moderate depth). (6) Periods of inactivity exceeding three seconds (deep anesthesia).

low voltage waves become superimposed on a background of high voltage waves with a low frequency. This is referred to as a *mixed pattern*. As the concentration of the drug in the brain increases the voltage and frequency both begin to decrease. Periods of inactivity interposed between periods of activity are seen. Such inactivity separated by bouts of activity is called *burst suppression*. The interval of inactivity becomes longer as anesthesia deepens. Simultaneously the number of waves in each period of activity decreases also. Finally as inactivity of the brain appears there is a flat tracing of low voltage or a very slow rhythm. Recovery of activity promptly follows a decrease of the blood level (with volatile drugs).

Many things may alter the electroencephalogram and nullify its effectiveness. The absence of oxygen or carbon dioxide may reduce the activity and confuse the picture.

Various anesthetic agents have been studied for the cortical activity. The depths of anesthesia for various drugs have been categorized by Bickford, Faulconer and his associates into areas known as levels. Ether anesthesia manifests seven levels; thiopental five levels; cyclopropane six. In general a basic pattern characterizes most agents; the pattern varying with each individual agent as anesthesia deepens. Certain impotent agents, such as nitrous oxide, do not yield a pattern with well demonstrated levels unless more potent drugs are combined with them or anoxia is present.

ELECTRICAL ANESTHESIA

Anesthesia may be induced by means of electric currents. Burge found it possible to anesthetize animals by placing

a cathode at the head of an animal and an anode in some posterior position. Others have reported similar findings inducing electronarcosis by a variety of means. These cannot be discussed here. Generally electronarcosis may be produced in either one of two ways, (1) by the use of a substantial instantaneous shock or (2) by passing a low voltage current constantly through the body. In either case anesthesia depends upon amperage but since the current which flows depends upon resistance and voltage the magnitude is expressed in terms of voltage. Carefully controlled alternating currents (60 cycles of a strength of .3-1.2 amperes) are passed through electrodes placed over the temples of mental patients in electroshock therapy. In this treatment consciousness is lost and convulsions develop.

A current flowing into a nerve is capable of blocking an impulse passing through it. It is possible to use a high frequency, low amperage current to render a nerve inexcitable. To date such procedures have been limited to experiments in laboratory animals and have only limited application to man.

Anan'ev, a Russian, and his co-workers have described a method of inducing electrical narcosis by using two currents simultaneously—a direct and an alternating. Volpitto and his co-workers have verified these findings and were able to produce anesthesia which was satisfactory for operative procedures in dogs. The instrument employed is so constructed as to deliver through a common electrical lead a direct and alternating current. This current is so modified that when visualied on an oscilloscope produces a rectangular wave of 1 to 1.4 milliseconds duration, at a frequency of 100 impulses per second. The subject is in the cathode circuit of the output tube in order to provide a constancy in voltage despite the changes in resistance in the body. The instrument is capable of delivering 40 or more volts and 40 or more milliamperes. Obviously the instrument includes an oscilloscope to permit constant visualization of the wave formed and the frequency.

Recently Hardy and his co-workers have obtained anesthesia in humans using a frequency of 700 cycles per second, at 30-40 volts and a current of 10-25 milliamperes. Volpitto states that narcosis in animals and in man appears to be a function of the total amperage, the wave form employed and the arrangement of the wave form. All investigators of electrical narcosis have had difficulty in maintaining constant electrode contact with the subject. Such contact is necessary to maintain anesthesia. Painful stimulation develops if the electrical circuit is broken and re-established by improper contact. In Anan'ev's experiments, and also in Volpitto's, the pattern of current application is important for satisfactory induction. Induction is slow and commenced with an alternating current of 100 waves per second of a 1/10 millisecond duration and a current of 2-3 milliamperes. The current is gradually increased in increments.

The signs commonly employed to determine depth of general anesthesia are not applicable to electrical anesthesia. The only clinical evidence of anesthesia is the lack of response to painful stimulation. Animals swallow and react to auditory stimuli. Post-electronarcosis analgesia persists for quite some time, even up to an hour after removal of the current.

DEPRESSION OF CENTRAL HUMORAL MECHANISMS BY NARCOTICS

Drugs may exert their effects by modifying the activity of organ specific substrates which have a specialized function. Norepinephrine, serotonin and acetyl choline are neurohormonal substrates which are organ specific and are an integral part of activation of centers in subcortical structures. Serotonin and norepinephrine are present in bound form concentrated in areas which have been referred to by Hess, Brodie and others as the trophotropic and ergotropic systems. Hess postulated that the ergotropic system integrates mechanisms that physiologically involve body work and energize the body. Activation of this system causes increased sympathetic responses, induces arousal, and activates psychic states. The trophotropic system opposes the ergotropic and promotes activity of restorative and protective processes. Activation of the trophotropic system increases parasympathetic effects, decreases skeletal muscle activity and lowers responsiveness to external stimuli. A condition akin to sleep results. Reserpine appears to stimulate the trophotropic system. Lysergic acid diethylamide (LSD) produces effects suggestive of ergotropic stimulation. There is considerable evidence to support the thought that serotonin is the neurohormone of the trophotropic system and norepinephrine of the ergotropic system. Reserpine impairs the capacity of the cells to bind serotonin in the brain. It also has the capacity to release norepinephrine peripherally. The stores of norepinephrine become depleted and the sympathetic nervous system cannot respond to stimulation. Since chlorpromazine blocks both the central and peripheral action of exogenous norepinephrine it is believed to antagonize the action of norepinephrine in the brain. Sedation and relaxation result. A drug may elicit the effects typical of activation of the ergotropic syndrome in one of two ways: (1) by blocking the trophotropic system and unmasking the ergotropic or (2) by directly stimulating it.

These thoughts on neuropharmacology are interesting, but it must be remembered that they are rudimentary and provide little information concerning narcosis at this time. Perhaps future investigation will provide clues to the mechanisms involved in central nervous system depression.

CONCLUSIONS

It is obvious from the foregoing that the experimental evidence available does not adequately support any definite mechanism for the action of chemicals in causing narcosis.

Effects of Anesthesia Upon Composition of Body Fluids

AQUEOUS ENVIRONMENT OF THE CELL

THE PRECEDING CHAPTER has dealt with the mechanisms of functional changes occurring within the cell caused by anesthetic drugs. Many of the alterations of intracellular processes are influenced by changes in the environment of the cell. Unicellular organisms of the protozoan type function as individual self-sufficient units in an aqueous habitat. The cell, bathed constantly by this aqueous medium, derives oxygen and metabolites from it and eliminates carbon dioxide and other waste products into it. The metazoan type of cell is similar to the protozoan type in this respect. It differs from it, however, that it no longer is self-sufficient. Groups of cells have now been organized for specialized function. The aqueous medium surrounding the cells continues to be present in the higher forms of life but instead of being in an open space of a comparatively wide expanse is now confined in a contracted one of limited volume—the intercellular or interstitial space. The freedom of constancy of composition provided by the wide expanse of media for the unicellular organisms could not exist in the case of multicellular structures were it not for introduction of a new system to the scheme—the blood vascular system. The blood vascular system acts as a "go-between" for the interstitial system and the external environment.

DISTRIBUTION OF WATER IN THE BODY

The *total body* fluid in higher forms of life exists in *three separate areas*, often referred to as *compartments:* the *vascular space*, the *interstitial fluid* space, and the *intracellular* space. The interstitial fluid acts as an intermediary between the cells and blood. The fluid contained therein is undergoing continual variation of composition and volume.

EFFECTS OF ANESTHESIA ON INTRACELLULAR FLUID VOLUME

A constant interchange of substances is occurring between the fluid contained in each of the three compartments. A state of osmotic equilibrium exists between the cell and the interstitial fluid. The shift of water and other substances between the interior of the cell and the external environment varies with the activity of the cell. Increased activity usually is accompanied by an inward migration of water; a decreased activity, the reverse effect, or dehydration. Muscle cells imbibe water when activity is increased. Presumably, the water exchange is prompted by the exchange of metabolites necessary for cellular activity. Since narcotics depress cellular function, one would expect a transfer of fluid from the cell to the interstitial space. This seems to be the case from the data available. Barbour noted an increase in

water content of the brain of rats following the withdrawal of morphine. This withdrawal of the drug may be likened to a reversal of narcosis. A similar phenomenon has been observed following withdrawal of morphine in dogs. In other studies, in which the ratio between water content of the medulla and cerebrum was used as the criterion of cellular hydration or dehydration it has been found that dehydration occurs. The medulla contains fewer cells than the cerebrum so that any intracellular water shift is more apparent in the cerebrum. Rats and rabbits anesthetized with ether, amytal, and morphine, showed an increase of the medulla-water/cerebrum-water ratio. An increase in this ratio indicates a decrease of cerebrum cell water or dehydration. Brezina, Gallup and Barbour, in studies on rabbits narcotized with amytal, found an increase in water content of the medulla and a decrease in the cortical cells. Calculations of intra- and extracellular water from determinations of chloride ion of plasma confirmed these findings. Thus, much of that data available supports this view. Whether or not these findings are applicable to man is a matter of speculation which awaits the development of techniques which can be used in the intact animal or in man. Apparently during narcosis a dehydration of nerve cells occurs.

EFFECTS OF ANESTHESIA UPON BLOOD VOLUME

The constant interchange which occurs between fluid in the interstitial space and blood depends upon two forces—the *hydrostatic pressure* and the *osmotic pressure* (Chap. 2). The capillary blood pressure tends to force fluid through the capillary wall. However, the osmotic pressure exerted by the plasma colloids in the blood tends to overcome this force and draws fluid back into the vessel. The arteriolar and capillary blood pressure is greater than the capillary osmotic pressure, while in the venules the reverse is true. Fluid, therefore, filters continuously from the capillaries into the tissue spaces and from these spaces back into the venous circulation.

CONSTANCY OF COMPOSITION OF BLOOD

The *interstitial fluid* volume is approximately three times the blood volume. The volume and the composition of the blood remain remarkably constant even though many substances are passing continuously from and into the vascular space. This constancy of volume and composition of blood is maintained, when circumstances are normal, by certain well-balanced mechanisms. The lungs take care of the elimination of gases and other volatile substances to the outside atmosphere; the kidney and skin eliminate excess water, electrolytes and unwanted organic substances; the liver stores and filters or synthesizes new substances; the spleen stores cellular elements and discards blood pigments; the muscles store fluid and other elements. It is well-recognized that anesthetics may upset these various organic systems which maintain the composition of the blood at a steady state. The rate of circulation, the gaseous interchange in the lungs, the functions of the liver and kidney, the volume of the spleen, absorption and elimination from the skin and gastrointestinal tract—all may change during anesthesia. Permeability of the endothelium may be altered. Usually it becomes more permeable. This results in a migration of fluid and electrolytes from the vascular space into the interstitial

space and a subsequent change in the cellular composition.

Both the blood cells and plasma contain organic and inorganic constituents which under normal circumstances are in a delicate balance. Anesthesia may disturb this balance between constituents of cells and plasma, which in turn is reflected in the cells of the tissues. The blood constituents subject to changes in concentration are *the carbohydrates, the lipoids, the nitrogen-containing substances* and *the electrolytes.* Blood nitrogen may be divided into 2 fractions—that contained in *the protein* and that in *non-protein* substances. Protein concentration varies with fluid volume. It is, therefore, affected by anesthesia. Uric acid, urea, ammonia, amino acids, creatine and creatinine comprise the chief non-protein nitrogen substances whose concentrations may vary with anesthesia. Inorganic constituents include *anions* and *cations* of alkali and alkaline earth metals. The cations are *sodium, potassium, hydrogen, calcium* and *magnesium.* The anions are *sulphate, phosphate, chloride, bromide,* and *iodide.* In addition the blood also contains *vitamins, enzymes,* and *hormones,* as well as *bile salts, pigments* and *gases.* These may also be affected by anesthetics. The influence of anesthesia and related factors upon these is discussed in detail later.

BLOOD VOLUME

The *blood volume* of man is approximately 1/10 of the body weight. The blood volume is 1/10 of the body weight in infants as well as in adults. A 70 kilogram man has probably 6 to 7 liters of blood. Forty-five to 47% of the blood volume is cells, the remainder is plasma. No absolutely accurate method of measuring total blood volume is known. A number of methods are employed clinically. The *most common method, is injecting a* known concentration of a stable dye rapidly into the blood and measuring the dilution colorimetrically. The dye used must not diffuse into the cells or from the vascular space, nor must it be metabolized or cause hemolysis. Congo Red and Evans Blue have these properties. The latter has been used extensively. Since the dye does not pass into the cells the *plasma volume* is the volume measured. Another technique which employs carbon monoxide measures the red blood cell volume. A known volume of gas is inhaled and its distribution in blood is determined by estimating the quantity of carbon monoxide hemoglobin complex. At present the trend is toward using radioactive isotopes with short half-lives. Phosphorous tagged red cells or albumin to which has been adsorbed radioactive iodine or chromium are injected and the dilution is determined by physical methods of detection of radioactivity. In any case the total blood volume may be computed from the cell and plasma volume percentage. Cell volume plus plasma volume equals the *total blood volume.* If one knows either cell volume or plasma volume, he may calculate the total blood volume from the *cell and plasma volume percentages.* Both cell and plasma volume percentages are estimated by the *hematocrit* determination. In determining the hematocrit, blood is treated with an anticoagulant and centrifuged in a calibrated tube. The ratio of supernatant plasma to cells is estimated directly by reading the percentages off the calibrated tube. Micropipettes are available which use one drop of blood. The hematocrit *is used as an index of* changes in blood volumes. As such it may give a clue to changes in volume, but

may be grossly misleading. A fall in the percent of red cells may follow restoration of blood volume by hemodilution after hemorrhage as fluid is withdrawn from the tissues into the vascular bed.

In addition to the hematocrit, there are several tests which may be employed to determine whether or not hemoconcentration or hemodilution has occurred, such as determination of *hemoglobin content* or *blood specific gravity*. Hemoglobin determinations should be done simultaneously with hematocrit determinations because the volume of the cell may change from a loss or gain of water due to changes in reactions of blood. Specific gravity of whole blood or plasma is measured by the falling drop method of Barbour and Hamilton using brombenzene and xylol, mixed in certain specified proportions and placed in a tube through which a drop of blood or plasma of an accurately measured volume falls. The technique of Van Slyke using copper sulphate may also be used. The rate of fall is compared to that of a drop of a standard solution of known specific gravity. The specific gravity is either calculated or interpolated from a prepared table. *Total plasma protein* concentration may be computed indirectly from plasma specific gravity. *Total serum protein* may be determined by direct methods as the Kjeldahl or colorimetric methods.

MIGRATION OF IONS

Although *water shifts* from the plasma to the intracellular spaces and into the cells, it never passes from one space to another by itself. Electrolytes always diffuse along with it (Chap. 1). Sources of body water are (1) fluid ingested by drinking, (2) fluid in food, and (3) endogenous water produced by oxidation of food. Loss of fluid from the vascular space results in hemoconcentration. This

loss is characterized by a decrease in plasma volume and an increase in protein, hemoglobin, cell volume percentage (hematocrit), and specific gravity. Passage of fluid into the vascular space results in hemodilution. Dilution of blood is usually manifested by findings reverse to hemoconcentration.

FACTORS ALTERING BLOOD VOLUME

Blood volume is subject to variations from both changes in normal physiology and from disease as well. Hemorrhage, anemia, dehydration, shock, exposure to cold, and changes in posture (from recumbency to upright) cause reductions in blood volume. High temperature, muscular exercise, excitement, splenomegaly, liver diseases, leukemia, and hyperthyroidism are some conditions which may be accompanied by an increase in blood volume. Alterations in blood volume occur from anoxemia. This is due to constriction of the spleen and changes in capillary permeability. The latter causes loss of plasma into the tissue spaces.

EFFECTS OF ANESTHESIA UPON BLOOD VOLUME

Data from studies in blood volume in man during anesthesia are difficult to evaluate. An increase in the solid elements of the blood may be due to a variety of factors. Isolated studies on cell volume percent, blood specific gravity, hemoglobin, and the like do not necessarily reflect the status of the total blood volume. A coordinated study is needed in which the plasma volume, total blood volume, cell volume percent, and hemoglobin concentration are known.

Factors Other Than the Drug

During anesthesia a decrease in total blood volume occurs as a rule. Most

of this is due to a decrease in plasma volume. The cell volume percentage is increased and hemoconcentration is the result. The changes may be due to factors other than direct effect of the drug. Water intake and formation may be decreased, particularly under deep general anesthesia. Urine formation is usually suppressed. Fluid loss through the skin usually decreases due to lowering of body temperature and alterations of environmental temperature. Pulmonary ventilation may contribute to water loss although it usually accounts for only a small part of the total loss. Splenic volume varies during anesthesia. This in turn causes changes in cell volume percentage. The composition of the blood may also be changed. This in turn causes variations in osmotic pressure and blood volume. Capillary permeability may also be changed by anoxia, or reflex stimulation. The operation itself may also cause or superimpose changes.

Effect of Anesthetic Drugs

The influence of the anesthetic agent per se is not easily assessed. All agents appear to cause some decrease in blood volume. *Ether anesthesia* is followed by hemoconcentration, an increase in cell volume percentage, and a decrease in total blood and plasma volume. Barbour and Bourne found a 10% to 15% increase in blood concentration in dogs. Winter and Bourne also found an increased blood concentration estimated by change in specific gravity in dogs. Hamburger and Ewing found a 15% increase in hemoglobin content and a 10% increase in electrocyte concentration in dogs anesthetized with ether. Mann also found a reduction in blood volume in dogs using a technique of bleeding. McAllister found a lowering of plasma volume in dogs, averaging 11%. An increase in hematocrit

was observed concomitant with change in plasma volume. Stewart and Rourke, examining patients undergoing operation under ether anesthesia, observed a reduction in blood volume of roughly 13%. The concentration of blood constituents, such as protein, sodium and chloride ions, was maintained with little or no change. Bonycastle likewise noted a decrease with ether. Similar data have been reported by many using radioisotope techniques.

Role of the Spleen

The spleen plays a role in causing blood volume changes during anesthesia. Ether anesthesia causes the spleen to constrict. Light ether anesthesia in dogs causes an increase of cell volume and a decrease in plasma volume. After splenectomy the increase in cell volume is not as great. The hemoconcentration observed during ether anesthesia is explained by the fact the erythrocytes are extruded from the spleen when it contracts. Searles noted an increase in cell volume, hemoglobin content, and erythrocytes and platelet counts during ether anesthesia in dogs. After removal of the spleen the increase in cellular elements was only approximately half as much.

Derra reported a decrease in blood volume during *tribromethanol* narcosis. A decrease also occurs during *chloroform* anesthesia. A slight increase in cell volume percentage occurs during *cyclopropane* anesthesia. Seevers and his coworkers report an increase of 4% over the control level. Robbins has observed an increase in oxygen capacity during cyclopropane anesthesia in dogs. This suggests that hemoconcentration has occurred. Fay, Andersch, and Kenyon likewise noted an increase in cell volume percentage during cyclopropane in dogs. These findings also suggest that hemo-

concentration occurs. Similar findings have been noted in man.

Variable results have been reported in blood volume changes during basal narcosis with barbiturates. The most consistent results have been obtained using amobarbital. Bourne, Bruger and Dreyer recorded a hemodilution in dogs anesthetized with amobarbital. Adolph and Gerbasi, and Searles and Essex have reported similar results. A reduction in cell volume and hemoglobin concentration also occur. Moher reported a hemodilution in using barbital and pentobarbital. The dilution may be due in part to dilatation of the spleen which occurs during narcosis with barbiturates. Plasma volume is increased, however, during amobarbital anesthesia. The hematocrit is not as markedly changed after splenectomy during amobarbital anesthesia. Hamlin and Gregerson also found an increase of approximately 10% in plasma volume in using *pentobarbital* in cats. Thiopental used as a sole agent causes no change or hemodilution. In cats, *morphine* causes a loss of water from both plasma and whole blood. During *spinal anesthesia*, there is only a slight change in composition of the blood and in total blood volume.

EFFECTS OF ANESTHESIA ON INTERSTITIAL FLUID VOLUME

Determination of Interstitial Fluid Volume

The volume of interstitial fluid is not easily determined. The current methods give widely divergent values ranging from 16 to 30% of the body weight of normal male adults. The difficulties in determination are due to a lack of a suitable substance for the test. Such a substance should diffuse readily and rapidly from the vascular bed, should be excluded from the cells, should not bind with the protein of tissues, should have a slow rate of excretion compared to distribution, and should be inert in the body. Radioactive sulphur (S^{35}), as the sulphate ion, appears to possess most of the forementioned ideal characteristics. Formerly potassium thiocyanate (KCNS) was used.

Interstitial fluid volume is estimated by injecting tagged sodium sulphate into the blood. The sulphate or thiocyanate ion passes into tissue spaces. If the circulating blood volume is known, the dilution of the sulphate or thiocyanate injected into the blood can be computed. The volume of fluid needed to dissolve the thiocyanate or sulphate minus that of the circulating blood equals the interstitial fluid volume.

Distribution of Interstitial Fluids

The interstitial fluid volume is about 20% of the body weight. The quantity of water varies in different tissues. In the skin, for example, the extracellular water is approximately 43% of the weight of the tissue, kidney 57%, lung 49%, liver 37%, and muscle 13%. Interstitial fluid is an ultra filtrate of serum and contains the various electrolytes common to the extracellular fluids. Intra- and extracellular fluids are in osmotic equilibrium. The cells contain potassium as the principal base. The interstitial fluid abounds in sodium. The integrity of the cell, osmotically speaking, must always be maintained regardless of changes in ionic concentration of the environment. An increase in osmotic pressure in the interstitial fluid caused by changes in electrolyte content is accompanied by a shift of water from the interior of the cell to the exterior. In this manner, the osmotic pressure of the

cell is activated while that of the exterior is reduced until an equilibrium is established. Generally the composition of the cellular protoplasm does not change significantly unless the composition of fluid outside the cell is greatly out of balance. The interstitial fluid, besides acting as a buffer between the cells and the vascular space, also acts as a reservoir for fluid which can be mobilized in times of need. The plasma volume contained in the vascular space is, up to a certain point, maintained at a constant level at the expense of the interstitial fluid volume. Derangements in blood volume result when the interstitial fluid can no longer compensate for water loss occurs from dehydration, hemorrhage, or other causes.

EFFECTS OF ANESTHESIA ON INTERSTITIAL FLUID VOLUMES

Data on changes in interstitial fluid volume resulting from anesthesia are not plentiful. Barbour and associates noted a shift of water from the cells to the tissue spaces. Stewart and Rourke observed an increase in the interstitial fluid volume during surgery under ether anesthesia on human subjects.

Bonnycastle in studies mentioned in the previous section, noted a decrease in the calculated interstitial fluid space following *morphine-ether*, *morphine-atropine* and *ether*, and *thiopental* in dogs. Insignificant changes were found following *atropine*, alone and *cyclopropane*, and *nitrous oxide* anesthesia. The exact fate of the lost fluid was unexplained. It is interesting to note that barbiturates in these studies produced both an increase of plasma volume and a decrease of interstitial fluid. It is believed that barbiturates cause a migration of interstitial fluid into the vascular space. Crawford and coworkers found that the combination of thiopental and nitrous oxide in man caused an expansion of the extracellular fluid volume after anesthesia. Similar behavior was noted after cycloporpane and ether.

THE FORMED ELEMENTS OF THE BLOOD

THE ERYTHROCYTE

Anesthetic drugs cause some changes in erythrocytes. The erythrocyte has an average *diameter* of 7.2 microns, a thickness of 2.2 microns, an *area* of approximately 120 square microns, and a volume of 85 microns. The cell membrane is composed of protein and lipoid substances (lecithin and cholesterol). A sponge-like mass, known as the stroma, which is believed to be composed of the same substances as the membrane, holds the hemoglobin in its meshes. The water content of the red cell is less than that of other cells, usually averaging 60%. The hemoglobin is approximately 38% of the weight of the cell.

Erythrocytes have the same *osmotic pressure* as the surrounding plasma. The red *cell membrane is permeable* to certain substances but impermeable to others. Dextrose, water and urea may diffuse in either direction. The membrane is usually impermeable to cations (Na^+, K^+) except the hydrogen ion and to proteins of the plasma, as well as those contained in the cell. Bicarbonate and chloride ions pass through readily, though phosphate and sulphate do not. The red cell is subject to changes in size due to changes in pH of the plasma. Increased acidity of serum alters permeability of water and chlorides and allows migration of these substances into the red cells. Potassium is the chief base found in the erythrocyte.

EFFECT OF ANESTHETICS UPON THE RED BLOOD CELL

Anesthetic drugs effect the red cell in at least two ways. (1) They pass into the lipoid substance, since many drugs are lipophilic. (2) They alter the permeability of the membrane. Some anesthetic drugs, such as ether and chloroform, when added directly to drawn blood in vitro cause the red cells to hemolyze, particularly if the concentration is excessive. Apparently they alter the structure of the stroma by causing solution of the lipoids. In vivo, however, this does not seem to occur. The lipophilic anesthetic drugs, *chloroform, cyclopropane,* and *ethylene,* are found in greater concentration in the red cells than in plasma. The concentration varies with the red cell count. *Paraldehyde, ether,* and more water-soluble drugs are more evenly distributed between plasma and cells (see individual drugs for concentration). The concentration of the lipophilic anesthetics varies with the hemoglobin content for a given alveolar partial pressure of gas or vapor.

FRAGILITY DURING ANESTHESIA

Leake and his associates investigated the ability of red cells to resist hypotonic saline solutions after the administration of certain anesthetics to dogs. The *fragility* of cells in Simmel's solution (hypotonic solutions of electrolytes) decreased after a half hour's ether anesthesia. *Chloroform* anesthesia caused a prompt decrease in fragility. *Nitrous oxide* with oxygen and *ethylene* with oxygen produced only a slight lowering of resistance to hemolysis. *Carbon dioxide* was found to increase the resistance when dogs inhaled concentrations of 25% with any anesthetic drug. *Cyclopropane* anesthesia causes no change in resistance. *Barbiturates* cause a decrease in resistance to hypotonic saline solutions in vitro. This varies with the type of substituent. The hemolytic time of sheep's blood increases as the number of carbon atoms increase in the substituted alkyl radical when concentrations comparable to those found in narcosis are used.

HEMOLYSIS IN VIVO

Whether or not a red cell hemolyzes depends upon its water content, its critical volume, its ability to function as an osmometer, and the osmotic pressure within it. Hemolysis in vivo during clinical anesthesia is an unlikely occurrence. If it occurs, it is slight since only in unusual circumstances does one find an increase in serum bilirubin or other pigments, suggesting that hemolysis has occurred (except chloroform). Pure ether, ether in saline and large volumes of dilute nonisotonic infusion fluids of drugs may cause hemolysis. *Paraldehyde* rapidly administered intravenously to dogs produces hemolysis detectable by the pink color of the supernatant fluid of centrifuged blood. Solvents used for certain agents, as for example, propylene glycol may cause hemolysis. When excessive hemolysis occurs the hemoglobin spills into the urine.

FUNCTION AND CHEMISTRY OF HEMOGLOBIN

The chief function of the erythrocyte is to carry oxygen. This it does by virtue of the hemoglobin contained within it. *Hemoglobin* is a pigment derived from the heterocyclic substance, pyrrole. Four pyrrole nuclei unite to form a ring structure known as porphyrin. Side chains of various radicals may be added to this ring to form a number of types of porphyrin. One of these, known as *proto-*

porphyrin, forms the basis of hemoglobin. Porphyrins combine with metals to form *metalloporphyrin*. If porphyrin combines with *iron* in the ferrous state the metalloporphyrin known as *heme* forms. Heme combines with various nitrogenous substances, most important of which are certain proteins to form *hemochromogens*. When heme combines with the protein, *globulin*, hemoglobin results. Hemoglobin is a conjugated protein consisting of the colored pigment portion, heme, and the colorless portion globin.

UNION WITH OXYGEN

According to Granich the iron atom in heme is believed to be hexacovalent and this binds six atom groups. Four of these covalent bonds are linked together by nitrogen atoms of the globin molecule. The remaining one is free to combine with oxygen. The linkage with the protein and the nitrogen stabilizes the sixth remaining bond so that the oxygen cannot oxidize the iron to the ferric state. In this state only molecules which form covalent bonds with iron combine with the ferrohemoglobin. Oxygen and carbon monoxide form covalent bonds with iron without transferring electrical charges to the iron atom. They can combine with oxygen without altering the electrical neutrality. The iron atom thus is able to resist formation of hydroyl ions. Since hemoglobin contains 4 hemes it contains 4 atoms of iron which combine with 8 atoms of oxygen.

TYPES OF HEMOGLOBIN

Several types of human hemoglobin are known due to differences in the globin molecule. Hemoglobin F found in the fetus differs in electrophoretic mobility (movement in an electrical field) from that of hemoglobin A (adult type). They do not have the same oxygen dissociation curves and absorption spectra. Hemoglobin A has been resolved into three different components. Hemoglobin S is found in sickle cell disease. For further details the reader is referred to more comprehensive texts on the subject.

Approximately 15 grams of hemoglobin may be isolated per 100 ml. of human blood. A molecule of hemoglobin contains 4 atoms of iron. The iron portion, of the hemoglobin molecule, is 0.33% of its total weight. Oxygen combines with the iron portion of the pigment in such a manner that two atoms of oxygen combine with each atom of iron in a reversible equilibrium. Four percent of the hemoglobin molecule is heme, the remainder is globin. The *molecular weight* of *hemoglobin* is estimated to be 68,000. A fully saturated molecule of hemoglobin combines with 8 atoms or 4 molecules of oxygen.

OXYGEN CAPACITY AND CONTENT OF BLOOD

One unique feature of hemoglobin is its ability to rapidly absorb oxygen and to cling to it tenaciously at high oxygen tensions and to part with it easily when it is exposed to low tensions. The combination is not an oxidation but merely an *association*. Hemoglobin enmeshed in the stroma as it exists in the cell behaves differently from that which has been separated from the stroma and prepared in an aqueous solution. Dissolved hemoglobin readily combines with oxygen, but the ready dissociation at the lower oxygen tensions does not occur. The graphic representation of the dissociation of the solution if plotted at various oxygen tensions from 0 mm. Hg to 150 mm. Hg is a *hyperbola;* for the

hemoglobin in whole blood it is an S-shaped curve. Increases in temperature, hydrogen ion concentration, exposure, to reduced or zero oxygen tension favor the dissociation of oxyhemoglobin to reduced hemoglobin. One gram of hemoglobin in whole blood when fully saturated combines with 1.34 cc. of oxygen. In arterial blood 95% of the hemoglobin is oxyhemoglobin, the remainder is reduced. The inhalation of 100% oxygen increases the total amount of oxyhemoglobin to almost 100%. The amount of oxygen dissolved in plasma is about quadrupled, however. The tension in the blood is raised from 105 mm. Hg to over 500 mm. Hg. The pressure gradient, therefore, is increased considerably.

The volume of oxygen which can be liberated from a measured volume of blood is called *oxygen content*. Oxygen content is usually expressed in ml. of oxygen per 100 ml. of blood, or *volumes percent*. A normal adult who has 15 grams of hemoglobin per 100 ml. of blood, would have 15×1.34 ml., or 20.10 ml. of oxygen, if it were all oxyhemoglobin. The *dissolved oxygen* which amounts to 0.3 ml., must be added to obtain the total capacity. The blood content is only about 95% of this capacity. Venous blood contains less oxygen than arterial blood since the tissues utilize a certain portion as blood passes through the capillaries. The difference in volumes percent between the oxygen content of arterial blood and that of venous blood is known as the *arterio-venous or A-V difference*. Arterial oxygen content may vary from vessel to vessel because of differences in metabolic rate of a particular tissue. The true A-V difference is the difference between oxygen content of arterial blood and venous blood from the right side of the heart. Blood from

the right side of the heart contains an average mixture of all venous blood of the body. The A-V difference in man is determined by introducing a catheter under fluoroscopy through the veins at the elbow into the subclavian, and thence into the auricle.

DETERMINATION OF BLOOD OXYGEN

Oxygen capacity and *oxygent content* may be determined directly by use of the manometric apparatus of Van Slyke and Neill or the Scholander. Blood, drawn under oil or over mercury to prevent contact with air, is transferred to the apparatus and treated with an oxidizing agent such as potassium ferricyanide. The hemoglobin is oxidized to methemoglobin which causes the release of oxygen. The liberated oxygen is measured by absorption with sodium hydrosulphite and the *oxygen content* is computed in volumes percent (see Gas Analysis, Chap. 7). If a portion of the anaerobically collected sample is exposed to air or oxygen in such a manner as to allow all the uncombined hemoglobin to be converted to oxyhemoglobin and then analyzed, the *oxygen capacity* is obtained. The oxygen content divided by the oxygen capacity ($\times 100$) equals the *percent saturation* of the particular specimen. If oxygen capacity is divided by 1.34, the number of grams of hemoglobin per 100 ml. which can carry oxygen, is obtained. This method is perhaps the most accurate for determining hemoglobin but is too tedious and time-consuming for clinical use.

ALTERATION OF HEMOGLOBIN BY CHEMICAL AGENTS

Mild oxidizing agents, such as nitrites, ferricyanide, and chlorates convert the ferrous iron (Fe^{++}) of oxyhemoglobin to

the ferric state (Fe^{+++}). One oxygen atom is retained on the hemoglobin molecule but the remainder of the oxygen is released in gaseous form. Reduced hemoglobin also forms the same compound but does not give off oxygen. Hemoglobin oxidized in this manner is known as methemoglobin. Methemoglobin does not carry oxygen. Stronger oxidizing agents act upon the globin in addition to the heme portion of the molecule. The protein is denatured and the resulting compound is called *cathemoglobin*. Certain drugs cause the formation of methemoglobin in the living body but the pigment can again be reduced to hemoglobin by the body when these drugs are removed. Cathemoglobin cannot be converted to hemoglobin due to the fact that the globin is denatured. Cyanides combine with methemoglobin to form cyanhemoglobin, which is a non-toxic substance, comparatively speaking. This reaction forms the basis of detoxification of cyanides. Oxidizing agents are administered to cause methemoglobin formation in cyanide poisoning. Usually they are of little avail because cyanides kill so swiftly and there is no time for the changes to occur.

DISPOSAL OF ERYTHROCYTES IN THE BODY

Red cells are being constantly destroyed in the body. The hemoglobin saved is converted to other pigments. The heme portion is disrupted from the globin and freed of its iron. The iron is stored in the liver. The body conserves iron very judiciously. The heme is converted to various *porphyrins*. The reticulo-endothelial cells convert these porphyrins into the *bile pigments*, *bilirubin* and *biliverdin*. In these two pigments, the ring of the pyrrol nuclei is

disrupted but the pyrrol nuclei are retained in a chain.

IDENTIFICATION OF HEMOGLOBIN

Hemoglobin and related pigments absorb light of certain wave lengths and may be identified by spectroscopic methods.

Reduced hemoglobin is darker in color than oxyhemoglobin. A greater concentration than 6 grams of the reduced pigment per 100 ml. of blood, if conditions are proper, causes the appearance of *cyanosis*. Hemoglobin and oxyhemoglobin are both *weak acids*. However, oxyhemoglobin is more acid than reduced and usually exists as the *potassium hemoglobinate* in the cell. Hemoglobin combines with carbon monoxide in the same proportion as it does with oxygen to form a relatively stable compound, *carbon monoxide hemoglobin*. Carbon monoxide hemoglobin slowly dissociates to hemoglobin and carbon monoxide by exposure to high oxygen tensions. The dissociation is facilitated somewhat (about 3% per hour) by increasing the hydrogen ion concentration of plasma (by inhalation of 7½% CO_2). A stable compound forms between hemoglobin and nitric oxide (NO). Carbon dioxide also combines with hemoglobin to form a *carbamino compound*. The union, however, as the name suggests, is with the amino groups of the protein and not with the iron in the heme as in the case with oxygen and carbon monoxide. The linkage is represented as follows:

$$Hb{-}NH{-}\overset{\overset{\displaystyle O}{\|}}{C}{-}OH$$

"NORMAL" OXYGEN TENSIONS OF BLOOD

The *oxygen tension* in arterial blood (80-90 mm. Hg) is less than that in the

alveoli (105 mm. Hg) and that in the tissues is less than that of the blood.

Fetal blood contains considerably more hemoglobin than maternal blood. The *oxygen capacity* of fetal blood averages 22 to 23 volumes percent. Fetal arterial blood is approximately 50% saturated and contains 10 to 11 volumes percent of oxygen. The *oxygen tension* of fetal arterial blood is less than that of maternal arterial blood so that a gradient is established from the placenta to the fetus. The chemical nature of fetal hemoglobin is slightly different from the adult type, but the difference is not of significance as far as anesthesia is concerned.

OXYGEN TRANSPORT

The *transport of oxygen* during anesthesia must remain unimpaired, as every anesthesiologist realizes. Consequently, the effects of anesthetic drugs upon the oxygen combining power and dissociation of hemoglobin are important. If the airway is patent and the alveolar oxygen tension is well maintained, the oxygen content of arterial blood is not lowered during general anesthesia with currently-used anesthetic agents. No appreciable changes in the ability of hemoglobin to combine with oxygen or to release it have been demonstrated. One must bear in mind that anesthetic drugs are lipoid-soluble and may change relationships within the interior of the cell and affect the stroma which holds the hemoglobin in the cell. The *absorption bands* during the spectroscopic analysis of blood in the presence of *nitrous oxide* are slightly different from those of oxyhemoglobin. This has been interpreted to indicate a loose combination between hemoglobin and nitrous oxide. The question as to whether or not there is a combination

has not been settled conclusively. Other anesthetic drugs do not combine.

BLOOD OXYGEN ANALYSIS DURING ANESTHESIA

Analysis of the oxygen content of blood from anesthetized subjects is in some instances difficult because the anesthetic vapors interfere with the analysis. However, improvements in the methods by Seevers, Orcutt, Waters, Shaw, Dowing, Goldstein, Holladay and others, have extended the usefulness of the manometric apparatus of Van Slyke and Neill to anesthesia studies. Blood-oxygen-content determinations during anesthesia are now possible. Shaw and his co-workers undertook blood-oxygen studies in dogs anesthetized with *ether*. Both arterial oxygen content and oxygen capacity are slightly elevated when ether is administered by the open drop method. The increase in oxygen capacity may be an indication of an increase in cell volume percentage. The oxygen content of venous blood is also increased. The percent saturation is slightly lowered, particularly in view of the increased capacity in both arterial and venous blood. The A-V difference is narrowed, indicating that the tissues receive or use less oxygen. This indicates that tissues either require less oxygen, due to a decrease in metabolism, use less due to some unexplained effect on the oxidative mechanism, or the blood passes through the peripheral vessels at an increased rate.

The arterial oxygen content in man and dogs under *cyclopropane* anesthesia is also increased. The venous blood oxygen content rises and a narrowing of the A-V difference occurs. *Spinal anesthesia* in both man and dogs is accompanied by a normal arterial oxygen content but the

venous blood oxygen content is lowered. The A-V difference is widened, suggesting a stagnation of blood in the peripheral vessels. The oxygen content during anesthesia with *nitrous oxide* is within normal limits if the oxygen tension in the inspired mixture is not below that of the atmosphere. Similar data have been found for thiopental, halothane and other agents. Cullen and his associates noted no serious anoxemia when nitrous oxide with 20% oxygen was inhaled. However, when the mixture contained only 12%–15%, the oxygen content and tension in the arterial blood were reduced to *dangerously low levels*. The non-volatile drugs used for premedication may cause a lowering of arterial oxygen below usual values as a result of depression of the medullary centers. Such lowering occurs regardless of the fact that the inspired air contains 20% or more oxygen, unless respiration is assisted.

Effects of Anesthesia Upon Composition of Body Fluids (Continued)

EFFECTS OF ANESTHESIA UPON ELECTROLYTES, TOTAL BASE AND ACID-BASE BALANCE

CATIONS AND ANIONS

THE SOLUBLE inorganic constituents of tissues are largely crystalloids which are present in an ionized state. The cations are chiefly basic ions, the sum of which is often called *total base*. The most prominent cations are derived from the two alkaline metals, *potassium and sodium*, and two alkaline earth metals, *calcium and magnesium*. Other metals, such as zinc, iron, copper, cobalt and magnesium are present in traces in tissues. They exist as cations also. Some metals, as for example calcium, are bound to tissue protein and, therefore, are not included in the total base, since they do not pass into the soluble filtrate during analysis. The concentrations of these metallic ions or their salts are included along with the other cations in total base determinations. The ammonium ion is also present in blood. It also contributes to the total base since it is a cation.

The charges on the cations balanced by equal charges found on a group of anions maintain electrical neutrality. The anions are derived from both inorganic and organic acids. The most prominent anions in blood are *bicarbonate, sul-* phate, phosphate, chloride, bromide and iodide. This mixture of cations and anions is referred to as *electrolytes*.

MILLIGRAMS AND MILLIEQUIVALENTS

Concentrations of electrolytes are expressed in terms of milliequivalents (m.Eq.) in preference to milligrams per cent. In this system one deals with charges and not mass. A *milliequivalent* is the concentration of an ion per one ml. of a normal solution. It is computed by dividing the atomic weight of an element (or the sum of the atomic weights in a radical) by the valence of the element or radical. Twenty-three mgm. of sodium (atomic wt. 23) are equal to 20 mgm. of calcium (atomic wt. 40). One milliequivalent of a cation exactly balances one milliequivalent of an anion. The older method of expressing ionic concentrations according to milligrams per volume of fluid placed emphasis on the mass of the particle instead of charge. Therefore, such expressions yield no information regarding the potential for maintaining electrical neutrality. A chloride ion is as effective in balancing the charge on a cation as an ion derived from some protein which

may be several thousand times heavier. For example, one milligram of hydrogen (atomic wt. 1) unites with 17 milligrams of hydroxyl ion to give 18 milligrams of water or with 35 milligrams of chloride ion to give 36 milligrams of hydrogen chloride or with 68,000 milligrams of albuminate ion to give albumin.

TOTAL BASE

The total base of whole blood ranges from 150 to 160 m.Eq. per l. of which 138 to 148 are contributed by sodium, 5 by potassium, 5 by calcium, and 2 to 3 by magnesium. This total ionic charge is balanced by chloride 104 m.Eq., bicarbonate 26, phosphate 2, sulphate 1, and protein 17. There is an optimum concentration of each basic ion in a particular tissue or fluid. The organism attempts to maintain the concentration of each ion at this optimum level which is often referred to as a steady state. Mechanisms are present in the body which maintain a steady state and prevent an excess of ions from accumulating or a depletion by a rapid loss. The total base (cations) is an index of the total electrolyte concentration, since the concentration of anions, electrically speaking, must equalize that of the base.

The individual basic ions are not interchangeable one for the other. If one cation is depleted to any appreciable extent a shift or rearrangement occurs to offset the loss and maintain the electrical balance. Any appreciable shift usually results in discernible physiological disturbances. The concentration of individual anions may likewise shift but they may vary to a much greater extent before notable disturbances in body function are observed. This is not the case with the cations. The total concentration (anions), however, is as constant as that of the cations. A decrease in the total cations results in an equivalent decrease of anions or vice versa. The same applies to an increase of the total in either group.

OSMOLARITY

The osmotic force which develops across a semi-permeable membrane dividing a pure solvent from a solution is dependent upon the number of particles in a unit volume of solution (Chap. 3). The pure solvent tends to pass into the solution and increase the total number of molecules. One gram molecular weight of a non-ionizable substance, as for example glucose (180 gm.), contains 6.02×10^{23} particles. Such a quantity is termed an *osmol* since solution of this quantity of glucose in 22.4 liters of water depresses the chemical potential by one atmosphere. In other words, a pressure of one atmosphere must be applied to the solution to prevent migration of water across the membrane into the solution. One gram molecular weight of sodium chloride (58.5 gm.) contains 6.02×10^{23} molecules. This dissociates into two separate ions. Each ion is an individual particle and acts as such. The number of particles is doubled. Therefore, one molecular weight of sodium chloride exerts an osmotic equivalent of two osmols. Calcium chloride ($CaCl_2$) dissociates into three particles and exerts an osmotic effect of 3 osmols. The osmolarity of a solution depends on the number of particles, not on their size or charge. When a protein (albumin) chloride molecule dissolves in water it is divided into one protein particle (weight 68,000) and an anion (Cl) (weight 35). The osmotic effect of protein is similar in magnitude to that of sodium ion which is a far smaller particle.

The osmol is too large a unit to express osmotic forces found in biological fluids. The concentrations of osmotically active components of body fluids, therefore, are expressed in terms of milliosmols (m.Osm.) per liter or kilogram of water. One milliosmol is equal to 1/1000 of an osmol. One milliosmol of a monovalent ion is equivalent to one milliequivalent; one milliosmol of a divalent ion is equivalent to two milliequivalents of that ion.

OSMOTIC PRESSURE IN TISSUES

The transcellular fluids, interstitial fluids, and intracellular fluids have osmolal concentrations of approximately 300 milliosmols per liter of water. One m.osm exerts a pressure of 17 mm. Hg. Therefore, the total pressure generated in these fluids would be $300 \times 17 = 5100$ mm. Hg. Roughly 93% of the osmotic activities of plasma and body fluids is due to sodium, chloride and bicarbonate ions. When water moves across living membranes the shift involves the concomitant migration of electrolytes. Were not this the case a change in osmolarity would result.

INDIVIDUAL IONS

During anesthesia many factors operate that affect body water. Therefore, changes in concentration of cations and anions are to be expected if fluid balance is disturbed. The total base concentration may increase, decrease or it may remain unchanged. It may be possible, though, for the total base to remain unchanged while the concentrations of individual cations may vary. Loss of sodium ion, for example, may favor the retention of potassium without appreciably disturbing total base. Total base may increase or decrease as the result of changes in the concentrations of anions. The ions composing the total body electrolytes must therefore be considered individually as well as collectively.

SODIUM (NA⁺) ION

Distribution and Function

Sodium is a *monovalent cation* (atomic weight 23) which comprises approximately 92% of the total base of plasma. Sodium ion is distributed almost entirely in plasma and the interstitial fluid; 50% is extracellular, 40% is in bone and 10% is intracellular. That in bone is non-exchangeable. The concentration in plasma remains quite constant. It averages 140 m.Eq. per liter. Since sodium is largely an extracellular ion the concentration in whole blood is lower than plasma, averaging 70 m.Eq. per liter. Concentrations in whole blood vary with changes in the cell volume percentage. The kidney excretes sodium ingested in excess of body needs. When total base is depleted the loss is mainly sodium ion since this is the predominating basic element. Other basic cations may, but do not satisfactorily, replace depleted sodium either qualitatively or quantitatively. The total sodium ion concentration is proportionately so much greater than other basic ions that the influence of other cations, quantitatively speaking, is of little consequence in maintaining total base. Thus, the retention of potassium ion offsets depletion of sodium to a limited extent since the increase can be a little more than several milliequivalents and such an increase produces untoward responses.

The blood and tissue electrolyte concentration is under hormonal control, principally those of the adrenal gland. Other hormones which influence electro-

lyte balance are those of the posterior pituitary (antidiuretic) and insulin. Deficiency of adrenocortical hormones causes loss of sodium through the kidney and a retention of potassium. Sodium concentration in blood varies little in most diseases. Sodium is increased in renal disease, and in alkalosis. In Addison's disease and myxedema, plasma sodium values are decreased.

Effects of Anesthesia

Plasma sodium concentrations vary little during uncomplicated anesthesia. Both early and recent studies are in agreement and reveal few remarkable changes. Fay, Andersch, and Kenyon found only a slight change in blood sodium in dogs (2 to 3 m.Eq. per liter) after one hour's ether anesthesia. Marenzi and Gerschman also found practically no changes during ether anesthesia. McAllister, Foot, and co-workers likewise found *no change in sodium in dogs with ether.* A slight increase in sodium and total base was observed after cyclopropane anesthesia in dogs by Fay and co-workers. No change in total base after cyclopropane was reported by Grieschiemer. Changes in sodium concentrations are not due primarily to the effect of the anesthetic drug itself but result secondarily from aberrations induced by the anesthetic state. Disturbances in ventilation particularly *those causing* retention of carbon dioxide cause a shifting of sodium. Hydrogen ion quickly moves into the red blood cell and sodium and potassium move outward. The changes which are initiated during anesthesia may not become fully manifest until recovery. Salt retention, antidiuresis, changes in function of the tubules, impairment of absorption of water and changes in permeability of the endothe-

lial membrane are all factors which could influence sodium concentrations. During ether anesthesia an increase in sodium in the extracellular fluid spaces is noted.

One factor, upon which little emphasis has been placed, is the influence of disease states and electrolyte balance during and after anesthesia. Generally though, marked deviations are not observed in normal patients.

During anesthesia and surgery changes take place in the total volume of fluid in various compartments in the body. Despite this, the concentration of plasma sodium remains constant. Studies using radioactive sodium reveal a shift of sodium from the intra- to the extracellular fluid space. Anesthesia with cyclopropane causes a temporary suppression of electrolyte excretion which returns to normal during recovery. This is due to increased tubular absorption. The amount of sodium excreted is decreased even though *the urine volume is increased.*

POTASSIUM (K^+) ION

Function and Distribution

Potassium which, like sodium, is a *monovalent cation* is chiefly an intracellular ion. The total body potassium averages 45 m.Eq. per kilogram of body weight. A 70 kilogram man contains 120 grams of potassium. Approximately 60 m.Eq. or 2% of the total are found in the extracellular fluid. All of the tissue potassium is exchangeable and labile. It is possible to measure total body potassium by using radioactive dilution techniques. Studies with radioactive potassium reveal an almost complete turnover of the element in the body every few days. In blood, potassium is concentrated chiefly in the erythrocytes (107 m.Eq. per liter). Plasma levels average 5.0 m.Eq. per

liter. Whole blood, naturally, contains a much higher quantity than plasma. The range is 150 to 250 mgm. per 100 ml. or an average of 50 m.Eq. Within the cell potassium acts in the same manner as does sodium in the extracellular fluid. The ion influences osmotic pressure, acid-base balance and water retention.

Role of Potassium in Physiological Activity

Potassium ion is of extreme importance in the execution of various physiological processes. Potassium is abundant in nerve (530 mgm. per 100 gm.) and muscle (250 to 400 mgm. per 100 gm.). The ion, together with sodium and calcium, is essential in the maintenance of the heart beat. The potassium ion plays an important role in impulse transmission at the synapses in the ganglia, at parasympathetic (cholinergic) nerve endings and at the neuromuscular junction. Vagal stimulation is followed by an increase in potassium in perfusates from isolated hearts and other organs in which cholinergic fibres predominate. Potassium ion is essential for the proper functioning of acetylcholine at the synapses of ganglionic and other neurons. The ratio of the concentration of potassium in a resting nerve fibre is 5 parts to 3 in that of the surrounding medium. As the excitation wave passes along a fibre potassium migrates outward into the perineural fluid and sodium migrates inward (Chap. 21). During the recovery phase the reverse is true, potassium returns inward and sodium outward. This asymmetry in concentration of ions causes a potential difference to develop between the interior and the exterior of the cell. The interior of the membrane is negative to the exterior. Stimulation of

the nerve, or deprivation of oxygen, causes loss of potassium ions from the fibre and diffusion of the ion into the surrounding medium. The intraneural concentration returns to normal in the resting stage. Increasing the concentration of potassium in the medium surrounding the nerve causes a reduction of the electrical potential and a decrease in excitability of the nerve. Conduction may be blocked by elevating the extraneural concentration of potassium. A similar situation exists at the myoneural junction. Here, as in nerve, potassium ion predominates on the interior of the membrane and sodium at the exterior. The interior of the membrane is negative in relation to the exterior (Chap. 23). Lack of potassium results in asthenia and inability of the muscle to contract.

Variations in Plasma Levels

The concentration of potassium in blood remains remarkably constant in healthy adults. Ordinarily blood level determinations show little variations due to the remarkable constancy of the concentration in blood. The plasma level of potassium is a poor index of tissue stores of the ion. In acute renal failure, since the kidney cannot eliminate the ion, the discharge of small amounts of potassium from the cells results in excessive potassium levels. The concentration may rise to lethal levels (8–10 m.Eq. per liter). In diabetic acidosis, when renal function is normal, much of the cellular potassium migrates outward into the extracellular fluid. However, it is excreted into the urine and little change in potassium level occurs. The plasma level therefore is misleading. The infusion of glucose causes the transfer of potassium into the cells and results in a sharp decline in plasma potassium. Potassium ion causes

toxic symptoms when the extracellular concentrations exceed 1/10 to 1/8 of that normally found intracellularly. Potassium salts are rapidly absorbed from the gastrointestinal tract. The normal functioning kidney quickly excretes excesses ingested over the immediate needs of the body.

Variations with Disease

Blood levels vary in some disease states. In anemias blood levels are below the stated normal due to reduction in cell volume. In polycythemia blood levels are above stated normal values due to the increase in total number of red cells. Scudder and associates observed a rise of serum potassium in intestinal obstruction. Serum potassium is increased in Addison's disease and other disturbances associated with hypofunction of the adrenal. The increase occurs in the extracellular fluid due to decreased renal excretion resulting from loss of sodium ions. Whether or not the cortical hormone of the adrenal gland controls potassium levels as they do sodium has not been established with certainty. However, the concentration of both ions is interrelated—the concentration of one influencing the concentration of the other. Release of epinephrine and norepinephrine causes an increase in plasma potassium. This is released from the liver as a result of the glycogenolysis caused by increased sympathetico-adrenal activity. Loss of sodium ions may result in an increase of potassium plasma levels. This occurs at the expense of intracellular stores of the ion. Therefore, changes in the concentration of one ion must be correlated with levels of sodium ion.

An excess of potassium ion in the blood produces disturbances in cardiac rhythm. The T waves are elevated. Hypopotassemia likewise causes changes in cardiac rhythm. Low voltage in the electrocardiogram and a flattening of the T waves are commonly observed. Retention of carbon dioxide causes an elevation of blood potassium. This is described further on. Potassium ions also tend to antagonize the effects of calcium.

Effects of Anesthesia

Alteration of serum potassium levels may occur during general anesthesia since concentrations of the ion are influenced by respiratory acidosis and respiratory acidosis may occur during anesthesia. Changes in total base, blood volume and cell permeability possibly contribute to the disturbance. Data of earlier workers is not in agreement with more recent figures. Greschman and Marenzi found the plasma potassium of dogs anesthetized with ether, chloroform, morphine and chloralose falls soon after induction of anesthesia and returns to normal after four hours. They felt that the ion migrates from the plasma to the tissues, and possibly to the liver, since there was no increase in the content in the red corpuscles. Robbins and Pratt also noted a fall which persisted for 30 minutes after termination of cyclopropane anesthesia. This was followed by a return to the normal levels after five hours. Andrews and co-workers also observed a fall with ether. Stewart observed an average fall of approximately 11% in man operated under ether anesthesia. Fay, Andersch, and Kenyon also noted a fall with both ether and cyclopropane in dogs. The fall was greater with ether than with cyclopropane.

Cattell reported a severalfold increase of potassium in sera of cats subjected to complete asphyxia for four to five min-

utes. *Dial,* which was used for anesthesia in these experiments produced a slight lowering of the potassium level. These findings are difficult to interpret since the concentration of the ion itself was studied and no correlation was made with concentration of other ions, plasma pH, and depth of anesthesia and so on.

It has been established recently that changes in serum potassium during anesthesia are directly related to the degree of retention of carbon dioxide. Young and his workers and Brown and his associates observed that a marked rise in potassium occurs when carbon dioxide is retained to a degree which resulted in severe respiratory acidosis. Abrupt removal of the carbon dioxide caused a rapid rise in potassium with a tendency towards ventricular fibrillation particularly during hypothermia.

CALCIUM (CA^{++}) ION

Distribution

Calcium is a *bivalent cation* present in extracellular fluid. The atomic weight of calcium is 40. Therefore, 20 milligrams per liter constitute one m.Eq. of the ion. The cation is indispensable for maintaining normal cardiac function, the integrity of the nervous system, and normal membrane permeability. It is necessary for clotting of blood and for the formation of calcium phosphates and carbonates in the bones, teeth, cartilage, and other rigid tissues. Calcium is the most abundant metal in the body. Ninety-nine percent of the calcium in the body is in the skeleton. Two percent of the weight of the adult body is calcium.

Absorption

The daily requirement for an adult is 0.45 gm. For a child, approximately twice this amount is needed. Absorption of calcium occurs mainly from the upper region of the small intestine. The more alkaline the intestinal contents the less soluble are the calcium salts and the less the absorption. Vitamin D promotes absorption from the bowel. Calcium is excreted into the large bowel continuously regardless of the calcium intake. If the phosphate to calcium ratio is high insoluble calcium phosphate forms and absorption is decreased. Small quantities of calcium are excreted in urine (approximately 150 mgm. daily).

Blood and Tissue Concentrations

The concentration of calcium in blood is related to and dependent upon the concentration of phosphates. The concentration in serum averages between 9 mgm. and 11 mgm. per 100 ml. (5 m.Eq. per liter). Erythrocytes contain only minute traces of calcium. The spinal fluid contains 2 m Eq. Muscle contains approximately 70–80 mgm. per 100 gm. of tissue (almost as much as plasma). Nerve tissue contains 15 mgm. per 100 gm. The blood concentration varies little during health.

Serum calcium exists in two forms—a *diffusible ionized* form and a *bound unionizable* form. The diffusible fraction varies from 50 to 60% of the total. Practically all the freely diffusible fraction is believed to be ionized (all except 0.25 mgm.). The unionized portion is believed to be physiologically inactive because it exists as calcium carbonate and phosphate both of which are inert. The concentration of diffusible calcium in blood is greater than that which can be accounted for by the solubility product of the ion and the anions which tend to precipitate insoluble calcium compounds, namely phosphate ions. Serum proteins probably assist in maintaining the calcium in solution. A definite rela-

tionship exists between the concentration of serum protein and serum calcium. This proportion is 0.556 calcium to 6 protein by weight. Blood serum is probably a saturated solution of calcium phosphate. The relationship between protein, calcium ion, and inorganic phosphates in serum is believed to be calcium 0.556, protein 6, and phosphate 0.225. The calcium combined with protein is probably bound with the albumin fraction and this fraction is only partially hydrolyzed. A decrease in protein causes an increase in diffusible calcium in blood. Inorganic phosphate probably has a suppressing effect, not only upon the ionized portion of calcium, but also upon the fraction combined with protein as well. An increase in sodium ion concentration causes a decrease in organic serum phosphate.

The amount of ionized calcium in the blood varies with serum pH. This relationship can be understood readily since the hydrogen ion concentration influences the serum bicarbonate and phosphate concentrations. A decrease in hydrogen ion concentration (alkalosis) causes the ionized calcium faction to decrease. An increase of hydrogen ion concentration (acidosis) causes a rise. The changes occur principally in the physiologically active calcium. Calcium ions decreased as bicarbonate or phosphate ions increase and increase if the concentration of bicarbonate and phosphate ions falls. Alkalosis and acidosis do not appreciably affect total serum calcium since changes in serum pH influence chiefly the ionized portion which is only a small fraction of the total.

Hormonal Control of Plasma Levels

The calcium stores of the body are profoundly influenced by *parathormone*, the hormone secreted by the parathyroid

gland. Excess parathormone causes an elevation of serum calcium. An excess of parathormone causes calcium to be mobilized from the depots in bones. The effect of parathormone is dependent upon an adequate supply of vitamin D. Extirpation of the parathyroid glands is followed by a decrease in serum calcium and an increase in organic phosphates. *A concentration of calcium in blood below 7 mgm. per 100 ml. results in tetany.* This syndrome may be relieved by injections of parathormone and calcium. Insulin and epinephrine cause transient changes in serum calcium which are probably due to a decrease in serum phosphate. Vitamin D aids in the absorption of calcium from the intestine and causes an elevation of the serum level. Vitamin D requires the presence of parathormone. Oral ingestion of quantities above the minimum daily requirement of calcium, on the whole, affects serum levels very little. A temporary rise may occur during the first two hours but this is followed by a return to normal within three hours. Likewise, diets low in calcium cause little change in serum calcium levels because the calcium in bones is mobilized under these circumstances and offsets deficiencies. Sulphates injected intravenously lower serum calcium temporarily.

Effects of Anesthesia

Little data is available on the effect of anesthesia on serum calcium. Some changes are to be expected since a number of factors upon which serum calcium depends, such as serum pH, bicarbonate and phosphate change during anesthesia. Overventilation may cause a reduction in total serum calcium if the carbon dioxide tension is reduced appreciably. This may be of sufficient degree to cause tetany. Some of the neuromuscular

phenomena accompanying acute anoxia have been ascribed to tetany resulting from hyperventilation which occurs initially. Ether anesthesia is accompanied by a lowering of serum calcium. A decrease has also been observed during narcosis from morphine and somnifen in animals. No change has been observed during tribromethanol narcosis. The changes reported during anesthesia however are slight and apparently of no biochemical significance since manifestations of hypocalcemia or hypercalcemia have not been observed.

MAGNESIUM (Mg⁺⁺) ION

Function

Magnesium is a bivalent cation whose atomic weight is 24. One milliequivalent, therefore, equals twelve milligrams per liter. Magnesium is an indispensible element in mammalian tissues. Apparently the ion plays a part in a number of physiological functions. Magnesium is essential for the maintenance of a proper state of neuromuscular activity. It behaves somewhat like calcium in this respect. It probably acts as a coenzyme in muscle to activate enzymes of the glycolytic system. Magnesium is essential as a coenzyme in the formation of hexose phosphate, the preliminary step of the breakdown of a carbohydrate.

Distribution in Tissues and Blood

Approximately 70% of the total magnesium in the body is present in the bones. Magnesium is primarily an intracellular ion. Most of that which is present in blood is in the corpuscles. The concentration in muscle is approximately 21 milligrams per 100 grams of tissue. Muscle cells contain more magnesium than calcium. The exact blood magnesium level is not easily established because the methods of analysis heretofore

have been complex and tedious. However, more is being learned about magnesium since the flame photometer has been used for analysis. The usual concentration in serum varies between 1.4–1.7 m.Eq. per liter. The concentration in whole blood is considerably higher, usually 2 mgm. to 4 mgm. per 100 ml. (1.7–3.4 m.Eq.). The average is 2.4 m.Eq. The concentration in cells is variable due to shifts in cell volume, but under normal circumstances averages from 6 to 7 mgm. per 100 grams of tissue. More magnesium is found in the cerebrospinal fluid than in plasma—about 3 mgm. per 100 ml. 2.4 m.Eq.).

Effects of Deficiencies and Excesses

Deficiency of magnesium is uncommon. Magnesium deprivation usually causes vasodilatation, hyperexcitability of the nervous system and tetany and similar neuromuscular phenomena. The tremors in chronic alcoholism are ascribed to magnesium deficiency. Fat metabolism may be disturbed and decalcification of bones may also occur. The plasma level is little more than a clue to the state of balance of the element in the body, since magnesium is an intracellular ion. The element cannot effectively replace calcium in bone formation. The magnesium in bones is not mobilized in deficiency states.

An excess of magnesium causes depression of the central nervous system. This action is of special interest to anesthesiologists. A plasma level of 5 mgm. per 100 ml. produces depression; 20 mgm. produces anesthesia. An excess can only result from parenteral administration, since magnesium salts are poorly absorbed from the gastrointestinal tract. Less than 2% of an orally ingested dose is found in the urine. Oral doses of the sulphate do not raise the serum level save in

the presence of renal disease. Injected magnesium salts cause an elevation in concentration of magnesium ion in extracellular fluid. This excess is subsequently excreted into the urine. Some of the magnesium is excreted in the feces. Excretion of a parenteral dose is rapid at first (4 to 8 hours), but gradually tapers off requiring a course of several days for complete elimination. Excretion of magnesium is delayed in the presence of renal damage. Magnesium is stored in the body, but the exact site of deposition has not been determined.

Effects of Anesthesia

Studies on variations of magnesium metabolism resulting from anesthesia are few. Any deviations which occur are apparently insufficient to cause physiological disturbances. Serum magnesium is lowered during ether anesthesia. The significance and the reasons for this are not known.

Magnesium Anesthesia

High concentrations of magnesium depress nerve activity as has been mentioned previously. This effect occurs both centrally and peripherally. Local application of a solution containing magnesium ion to a nerve produces a blockade. Presumably the magnesium acts by depolarizing the membrane. Magnesium salts injected intrathecally produce spinal anesthesia. This response is believed to be due to a change in tonicity rather than to a direct magnesium affect on the neurons.

Parenterally magnesium ion produces varying degrees of central depression depending upon the concentration in the blood. Magnesium salts are used to control hyperactive states of the nervous system, such as convulsions due to hypertensive encephalopathies. The action of sedative and anesthetic drugs is augmented by intramuscular and intravenous injections of magnesium sulphate. Combinations of subcutaneous morphine, rectal ether mixtures and intramuscular injections of 50% magnesium sulphate ($MgSO_4 \cdot 7H_2O$) have been used to produce anesthesia. A 2% aqueous solution is isotonic and suitable for intravenous administration. Plasma levels exceeding six times the normal level produce medullary paralysis and respiratory arrest. Variations in reflex activity can be correlated with blood levels. Magnesium anesthesia is not therapeutically useful since it is not controllable and vital centers are readily inactivated. The depression produced by magnesium ion may be reversed by calcium ion intravenously. Exactly how calcium salt exerts this effect is not understood. The reversal is not a direct antagonism, but rather the resultant of a selective action these ions exert on various portions of the brain, each ion acting in a different area. However, calcium does not completely protect or antagonize when magnesium levels are high. Either the chloride or the gluconate of calcium may be used. The magnesium apparently exerts its effect at the central or nuclear portion of the neuron.

Magnesium also exerts an effect at the neuromuscular junction. An excess of magnesium ion produces a curare-like effect. Presumably the amount of transmitter substance liberated (acetyl choline) is decreased by the presence of an excess of the ion. Calcium likewise antagonizes the magnesium effect and restores the output of acetyl choline. Both ions presumably influence, in an opposite manner, the release of acetyl choline from nerve endings. Cardiac automaticity is reduced somewhat by magnesium ion.

CHLORIDE (Cl⁻) ION

Distribution

Chlorine is an abundant element essential to life. In tissues this element exists as an inorganic monovalent anion whose atomic weight is 35. One milliequivalent of chloride ion equals 35 mgm. per liter of fluid. The total body chloride of a normal man averages 33 m.Eq. per kgm. of body weight. Chloride is mainly an extracellular ion. However, this is not strictly so. Approximately 30% is found in the cells and in the connective tissues. The intake of chloride is mainly dietary in the form of sodium chloride. The intake and output of chloride ion, therefore, is almost inseparable from that of sodium. Both ions, acting together, are essential for the maintenance of water balance, the osmotic relationships of blood and cells and the regulation of the hydrogen ion concentration of blood. Chloride ion readily diffuses into erythrocytes and muscle cells. Therefore, this ion is found in both the intra- and extracellular fluids. Diffusion into cells other than the erythrocytes also occurs but is insignificant. In these cells the chloride is probably associated with the protein. The concentrations of chloride ion in plasma, lymph, and interstitial fluid are approximately the same. The chloride content of erythrocytes is about half of that of plasma. In the cells, the ion is paired chiefly with potassium; in plasma with sodium.

Blood Levels

Whole blood, under fasting conditions, contains an average of 70 m.Eq. of chlorides per liter (between 450 and 500 mgm. expressed as sodium chloride per 100 ml.). The serum level is higher, the average values being 103 m.Eq. per liter (570 to 620 mgm. per 100 ml.). Concentrations in whole blood vary with the cell volume which in turn is largely dependent upon the bicarbonate content of serum and the pH of blood. Chloride ion shifts from the plasma to erythrocytes when blood hydrogen ion concentration increases and from the cell to the plasma when carbon dioxide is lost from blood (chloride shift). The decrease in chloride in the red cells is explained by the Donnan effect. The water content in the cell is decreased when carbon dioxide is lost.

The cerebrospinal fluid contains more chloride ion than plasma or other body fluids (124 m.Eq. per liter).

Serum chlorides are decreased during: (1) starvation, (2) digestion, (3) changes in respiratory activity and (4) in various diseases. During starvation the decrease is due primarily to reduced chloride intake. Acidosis may also play a role. During digestion the decrease is possibly due to the migration of chloride ion into the stomach as hydrochloric acid is formed. A return to normal follows later. This is presumably due to reabsorption. During changes in respiratory activity carbon dioxide retention occurs from rebreathing. This causes a migration of chloride into the cell and a decrease in serum chloride. In the initial stages of acute anoxemia hyperventilation may occur which causes a loss of carbon dioxide. This in turn causes a reduction in serum bicarbonate, and a shift of chloride from cells to plasma. Hyperventilation without anoxemia causes similar changes. The decreases in these cases are slight, however, and average approximately 0.3 m.Eq. to 1.0 m.Eq. per liter of serum.

Pulmonary insufficiency may influence blood chloride levels profoundly if carbon dioxide is retained. Emphysema is

usually associated with carbon dioxide retention and an increase in bicarbonate ion. The serum chlorides usually decrease and may be as low as 70 m.Eq. per liter. Decreases in serum chloride ion are also seen in burns, shock, pneumonia, and fevers. Serum chlorides are elevated in anemias of various types because the red cell volume percentage (hematocrit) is decreased. Serum chlorides are reduced almost 50% in cases of excessive vomiting from pyloric and high intestinal obstruction.

Chloride ion, of course, is lost with some of the cations since it cannot be lost alone. Clinicians speak of depletion of chlorides or depletion of sodium as though only one ion were lost. An anion always is lost with a cation. Hydrogen ion is the anion usually lost along with chloride in protracted vomiting. In chloride depletion the basic cations, mostly sodium and potassium, which remain in the blood are balanced by bicarbonate ion which forms from retained carbon dioxide. The blood pH rises, the carbon dioxide combining power is elevated, and the total blood carbon dioxide is increased. An alkalemia often referred to as hypochloremic alkalemia may result if the bicarbonate excess is not compensated for by loss of base through the kidney (see acid-base balance, this chapter). In Cushing's disease, after the administration of excess ACTH or cortisone, potassium is lost with a resulting hypochloremic alkalosis.

Effects of Anesthesia

Obviously, then, since serum chloride levels may vary as other factors vary, plasma chloride levels alone give little more than a clue as to what is going on in the electrolyte picture. During anesthesia, some of these factors, particularly those concerned with respiration, may be disturbed. It is not surprising, therefore, that changes in blood chloride should occur during anesthesia. Determinations of chloride in blood must be correlated with data on total base content of blood and fluid volume for correct interpretation. In many of the reports on the blood chlorides during anesthesia this correlation has not been made. Data of this sort, therefore, has very little meaning.

BROMINE AND THE BROMIDE (Br⁻) ION Distribution

Bromine is one of the four halogens. Bromine occurs in tissues in traces. It exists in the body largely as the bromide ion. The bromide ion is a monovalent anion whose atomic weight is 80. The exact role the element plays, if any, in the body is not known. Blood contains from 0.23 mgm. to 1.71 mgm. per 100 ml. The element is of interest because the bromide ion present in excess causes depression of the central nervous system. Bromides are used in medicine as *sedatives and hypnotics.* Usually the sodium, potassium or ammonium salts are used. The absorption of these salts is rapid. The cells, with the exception of the erythrocytes, are as impermeable to bromide ion as they are to chloride. Bromide ion diffuses through the erythrocyte in the same manner as does chloride. *Bromide ion may replace chloride* ion in extracellular fluid. This substitution does not appear to influence the function of the cells except nerve cells. Nerve cells apparently are sensitive to the substitution. As the concentration of bromides rises in the body fluids that of chloride falls proportionately, but the total concentration of halogen ion in milliosmols remains constant. The suggestion has been made that the result-

ing decrease in chloride ion causes the depression of the nerve cells. However, this is unlikely because decreases in chloride unassociated with the presence of bromide ion produce no depression. The nitrate ion may replace a large part of the chloride ion without any resultant depression. Apparently the pharmacological action on the nervous system is a property of the bromide ion itself.

Relationship to Chloride Ion

The bromide ion is handled in tissues in the same manner as the chloride ion. Tissues and the excretory organs do not distinguish between the chloride and bromide ions. The total halogen in terms of milliequivalents is maintained at a constant level in serum. The ratio of chloride to bromide in tissues depends upon the intake of each ion. Bromide ion displaces chloride from body fluids if injected in large amounts. The ratio of chloride to bromide ion in extracellular fluid equals the serum ratio. The ratio of the two ions in spinal fluid is less than in serum.

Elimination

Bromides, like chlorides, are eliminated by the kidney. The kidney maintains a constant ratio of each halide ion in blood without considering whether it is chloride or a mixture of chloride and bromide. Bromides are eliminated slowly because the body attempts to maintain osmolarity and can only do so by retaining the bromide ion along with chloride to balance the cations. On a weight basis bromide ions are present in a relatively smaller concentration and, therefore, a proportionately smaller amount is excreted. A high chloride intake favors the elimination of bromide. If the concentration of chloride ions is low, bro-

mides are retained to maintain an equilibrium between the two ions. Bromides pass into sweat, tears, milk, and other secretions.

IODINE AND IODIDES

Distribution

Iodine, one of the four halogens, is also an essential constituent of the body. Approximately 50 mgm. of iodine are contained in the entire body. Ten to 15 mgm. of the total are in the thyroid gland. The daily intake is 200 gammas per day. Of this 20–70 γ are excreted in the urine. Iodine exists in two forms in the body, as an inorganic compound, probably the iodide ion, and as an organically bound derivative. The organically bound iodine of plasma is concerned with thyroid function. The organic iodine probably represents that present in the protein and is probably of hormonal origin. The usual normal values for total iodine are 5–15 micrograms per 100 ml. Low values are found in myxedema, cretinism, and endocrine disturbances involving failure of thyroid function. Elevated blood levels are found in thyroid disease due to over-activity. Eight to 18 micrograms (1 microgram = 1 millionth of a gram) are normally present. Approximately 20% of the iodine in blood is in the inorganic form. The administration of iodine or iodides produces elevation in blood iodine in both normal and diseased individuals. The iodine concentration varies with activity of the thyroid gland and metabolic rate. Tolerance to iodine is increased in hyperthyroidism and decreased after thyroidectomy. The function of the thyroid gland may be determined by measuring uptake of radioactive iodine (131). Less than 20% uptake indicates hypofunction; 50% hy-

perfunction, while 30% is considered normal uptake.

Relationship to Anesthesia

No significant relationships have been found between iodine levels and anesthesia. Studies of blood iodine levels during and following ether anesthesia in rabbits have been performed, but conflicting data have been obtained. Studies in man are lacking. There is to date little evidence that any profound change occurs.

PHOSPHATES

Distribution

Phosphorus is an essential element found in all the cells of the body. Four general types of phosphorous compounds exist in the body: (1) *The inorganic forms*. Salts of orthophosphoric acid fall in this group. They form important anions in body fluids. (2) *Esters of phosphoric acid*. These include hexose phosphates and glucophosphates. About 80% of the total calcium is combined with phosphorus in the bones and teeth. The remainder is found in various chemicals of the body. The importance of phosphorous esters in the transfer of energy and in the absorption of carbohydrate and lipids has been mentioned elsewhere (Chap. 27). (3) *Phospholipoids*. Certain compounds are combined with lecithin, cephalin, sphingomyelin, and other lipoids. (4) *Nucleic acids*.

Organic esters are essential for maintenance of blood phosphates, carbohydrate metabolism, and as reserve stores of phosphorous. Phosphatides are concerned almost entirely in fat metabolism and transport of fat in blood. A continual shifting and interchanging of phosphorus occurs between inorganic and organic forms. This shifting probably results from variations in fat and carbohydrate metabolism and the loss of phosphate due to the changes in hydrogen ion concentration of blood. The discussion in this chapter is concerned primarily with the inorganic forms since they are instrumental in maintaining the neutrality of the blood.

Inorganic Phosphates

The inorganic phosphorus compounds (phosphates) are of chief interest to the anesthesiologist because they form anions in the electrolyte pattern of the blood which help maintain neutrality. These may be subject to variations in concentration as a result of anesthesia. The concentration of phosphorus as phosphates in blood averages 4 mgm. per 100 ml. in adults. The usual concentration is between 3 mgm. and 4½ mgm. (2.4 m.Eq. per liter). The concentration in children is slightly higher, between 4 mgm. to 6 mgm. per 100 ml. (3.7 m.Eq. per liter). The inorganic phosphates exist in two forms: disodium hydrogen phosphate (Na_2HPO_4), which is alkaline; and monosodium dihydrogen phosphate (NaH_2PO_4), which is acid. The concentration of basic phosphate in serum is four times that of the acid phosphate. Acids which pass into or form in the blood, particularly non-volatile acids, convert basic disodium hydrogen phosphate to the acid phosphate. As the acid phosphate in serum increases the excess is eliminated by the kidneys. The total serum phosphate remains constant because the body replenishes that which is lost from esters of organic phosphates. Thus, no change occurs in either the inorganic phosphate levels or the blood hydrogen ion concentration.

Blood Phosphate Levels

Serum phosphate levels may increase as a result of increased carbohydrate metabolism. After an intravenous injection of glucose, or a diet rich in carbohydrates, a rise in serum phosphate is observed. Epinephrine and insulin cause an increase of serum phosphate levels. Inorganic phosphates are believed to assist in the removal of glucose from blood in carbohydrate metabolism, probably by the formation of hexose phosphate ester. A decrease of serum phosphates occurs during the absorption of some fats. The effects of serum phosphates, serum calcium, and parathormone are interrelated. Parathormone causes an increase in the level of phosphates indirectly as a secondary effect to the direct control it exerts upon calcium. An excess of parathormone causes an elevation of blood calcium and a lowering of the phosphate levels. A deficiency of parathormone causes a decrease in serum calcium and an increase in inorganic phosphate levels. Pituitrin causes a rise in serum phosphorous.

The ratio between serum calcium and serum inorganic phosphorus, since calcium is precipitated by phosphates, is a fixed numerical value. The product of the concentrations of each element in mgm. per 100 ml. under normal circumstances ranges from 40 to 50. During the healing of fractures, serum inorganic phosphates are elevated.

PHOSPHATASE

The esterification and hydrolysis of organic phosphate ester is aided by enzymes known as phosphatases. These are necessary for satisfactory bone formation. Two types are present, an *acid* and an *alkaline* phosphatase. Phosphatases cause a hydrolysis of organic phosphoric esters and liberate inorganic phosphates for bone formation. The enzyme, thus, influences the regulation of inorganic phosphorous in the blood. The concentration of phosphatase in the blood is expressed in units. Normal values range between 1 and 6 units in adults and between 3½ and 11 in children (Robert's method of analysis). Serum phosphatase increases in certain bone diseases, in obstructive jaundice, and after high carbohydrate intake. Phosphatase levels in blood are influenced by hormones, particularly those which affect carbohydrate metabolism.

Effects of Anesthesia on Phosphorous Metabolism

A fall in total inorganic phosphates in blood of both dogs and man during anesthesia with *ether, chloroform,* and *ethylene* and other agents has been reported by early and recent workers. The suppression may persist for several hours after termination of anesthesia. The phosphate content of muscle decreases during anesthesia but the liver accumulates more than is normally present.

A decrease in excretion of urinary phosphate occurs during anesthesia. The excretion is increased in the recovery period. Recovery is characterized by subnormal blood levels. Pancreatectomy in dogs inhibits changes in blood phosphate levels. A decrease in serum phosphate may occur during morphine narcosis. Fay and co-workers found inorganic phosphate levels during ether anesthesia in dogs to be inconsistent. Marenzi and Gerschman found an increase in plasma phosphates during ether anesthesia. Magee reported an increase in rabbits. Greischeimer observed an increase in serum inorganic phosphate in dogs anesthetized with *cyclopropane*.

Apparently the inorganic phosphate content is quite variable in blood. Anesthesia influences phosphate levels by alterations in carbohydrate and lipoid metabolism or by the influence of liberation of hormones, such as *epinephrine*, which contributes to acidemia. As a matter of fact, the acidosis of ether anesthesia has been ascribed by Bourne to be due to a release of phosphoric acid into the blood.

LACTIC ACID

Physiologic Importance

Lactic acid is an *aliphatic hydroxy acid*. Structurally it is propionic acid with a hydrogen atom on the alpha carbon replaced by a hydroxyl group.

$$\begin{array}{c} CH_3 \\ | \\ H-C-OH \\ | \\ COOH \end{array}$$

Lactic acid is physiologically important because it is intimately concerned with carbohydrate metabolism. Lactic acid possesses an asymmetric carbon atom and is, therefore, *optically active*. Dextro lactic acid is more active physiologically than the racemic, or levo. Dextro lactic acid occurs in nature. Lactic acid contains carbon, hydrogen, and oxygen, in the same proportions found in glucose. The acid is formed from the breakdown of glucose through a number of complicated intermediary steps. Phosphoric acid is essential for the formation of lactic acid from carbohydrates. The transformation of glucose to lactic acid is an anerobic reaction which supplies energy for muscle activity. Lactic acid is reconverted to hexose by an aerobic reaction.

The whole blood of resting individuals contains anywhere from 10 to 20 mgm. of lactates, expressed as lactic acid, per 100 ml. A slight increase of lactic acid may occur during the injection of carbohydrates. In severe exercise lactic acid concentration in blood may rise from 50 mgm. to 60 mgm. per 100 ml. The acid which escapes from the muscle into the blood stream is reconverted into glycogen in the liver. Lactic acid exists in blood as lactate ion. The acid interacts with bicarbonate which is lost as carbon dioxide.

Effects of Anoxia

Anoxia is accompanied by a marked increase in blood lactates. Increases in lactic acid in blood cause metabolic acidosis if the lactate is not excreted or reconverted to glucose. Anoxemia and asphyxia reduce the available oxygen and prevent the oxidative recovery process which causes the conversion of lactates to glycogen. Therefore, lactates *increase in the blood and tissues*. In pulmonary diseases, such as pneumonia where there is oxygen deficiency, the *lactic acid in blood is increased*. In the early phase of acute anoxemia, hyperventilation may be present which causes a loss of carbon dioxide and a temporary alkalosis. This is soon followed by a metabolic acidosis due to increases in blood lactates. In cardiac disease, shock, hemorrhage, anemias, severe liver disease, heat exhaustion, and heat stroke, the blood lactic acid is increased as a rule.

Effects of Anesthesia on Blood Lactates

Blood lactates are increased during *general* anesthesia, particularly if carbohydrate metabolism is disturbed. The lactic acid formation and the hyperglycemia which follow *ether* anesthesia indicate that carbohydrate metabolism is disturbed. *Chloroform* anesthesia is also accompanied by a marked rise in blood

lactate. *Nitrous oxide* and *ethylene* anesthesia without anoxemia cause slight rises in lactates. If anoxemia complicates anesthesia, regardless of the drugs used, a rise in lactates occurs.

Phatak, in studying the fate of lactates which accumulate in blood of rabbits during *ether* anesthesia, noted that in the recovery period lactate is utilized to replace depleted liver glycogen. During anesthesia the mechanisms of utilization of lactates do not operate and they accumulate in the blood. Lactates injected by vein are utilized during recovery also. Sodium d-lactate is better utilized than the d-l under these circumstances. Lactic acid is not appreciably increased in *morphine* anesthesia without anoxemia. Slight increases in blood lactic acid may also accompany *cyclopropane* anesthesia.

SULPHATES

Distribution

Sulphur is present in all the cells of the body. Sulphur is important in tissue respiration (SH groups), in detoxification mechanisms, and in high energy sulphur bonds. Sulphur may exist in tissues in two forms: *organic* and *inorganic*. Organic sulphur containing compounds are usually present in the form of sulphuric acid esters of phenols. The sulphur in the body is probably derived from amino acids containing the element. *Cystine*, and *methionine* are the two *amino* acids containing sulphur. Elemental sulphur and inorganic sulphur are not sources of body sulphur.

Inorganic body sulphur occurs as the bivalent sulphate anion (SO_4) and is part of the electrolyte pattern of the body. Serum contains approximately 0.7 mgm. to 1.3 mgm. of inorganic sulphates calculated in the form of free sulphur per 100 ml. Sulphate content of whole blood is believed to be approximately twice this value. Sulphates are increased in obstructive jaundice, diabetes, and in certain liver and kidney diseases. No relationship of sulphates to anesthesia has been established.

EFFECT OF ANESTHESIA ON ACID-BASE BALANCE

STRONG AND WEAK
ACIDS AND BASES

In any solution of electrolytes the positive charges on the cations must be balanced with the negative charges on the anions in order to maintain electrical neutrality. The cations, as has been mentioned, are derived from metals and are, therefore, largely inorganic; the anions, on the other hand, are derived from both organic and inorganic acids. The ions which make up the bulk of the anion fraction are chloride, phosphates, bicarbonate, lactate, sulphate, proteinate, and hemoglobinate. These anions are derived from both strong and weak acids. The cations on the whole are derived from strong bases. A salt derived from a strong base and strong acid, that is an acid and a base each of which are highly ionized, forms an aqueous solution which is neutral to indicators. Solutions of salts derived from strong bases and weak acids are usually not neutral. The salt is highly ionized. However, the influence of the ions of water (hydrolysis) tends to form, a weak unionized acid and a strong base therefore predominates in the solution. Since the weak acid does not ionize to the same extent as the strong base the solution tends to have an excess of hydroxyl ions. Such a solution reacts basi-

cally to indicators. The following reaction illustrates the mechanism by which this hydrolysis comes about:

$$NaHCO_3 \rightarrow Na^+ + HCO_3^-$$
$$H_2O \rightarrow OH^- + H^+$$
$$NaOH \quad H_2CO_3$$
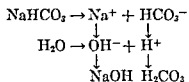
By the same mechanism a strong acid and a weak base form salts which are acid to indicators. The electrolytes in body fluids are chiefly of salts of weak acids and strong bases and are, therefore, due to the aforementioned effects of hydrolysis, alkaline. They have a pH greater than 7. This situation exists in blood. Blood is always slightly alkaline.

ACIDS IN BLOOD

Many end products of cellular metabolism are acids. The acids are either nonvolatile (fixed acids) or volatile. Hydrogen ion, therefore, is constantly being added to blood. With the exception of the small amounts lost in sweat and through the gastrointestinal tract, most acidic products formed during metabolism are eliminated by the lungs and by the kidney. The lung can only eliminate *volatile* acids while the kidney eliminates the *non-volatile*. The kidney, however, can eliminate both. The most abundant volatile acid and the one which is forming continuously is carbonic acid, since this results from the solution of carbon dioxide in plasma. Besides carbonic acid, phosphoric, sulphuric, lactic, and traces of numerus, less important ones, are formed during metabolic activity.

BUFFER PAIRS

The concentration of hydrogen ion in blood remains remarkably constant in spite of the fact that acids are being formed and are added continuously to the blood. An increase results in serious symptoms. A pH below 6.8 is not compatible with life. The mechanism which permits maintenance of a hydrogen ion concentration in a solution at a constant level is known as the *"buffer" mechanism.* The hydrogen ion combines with a chemical substance and is thereby removed from the sphere of activity. Substances which act as buffers and are capable of suppressing hydrogen ion concentration generally act in pairs. They are, therefore, termed "buffer pairs." Three general types of buffer pairs are present in blood. These are: (1) A salt derived from a strong base and a weak acid, which is paired with a weak acid. Sodium acetate would represent such a salt and acetic acid such an acid. (2) A salt of a weak base and a strong acid paired with a weak base. Ammonium sulphate would represent such a salt and ammonium hydroxide such a base. (3) An acid salt of a polybasic acid paired with a basic salt of a polybasic acid. Phosphoric acid is a polybasic acid and forms several salts among which are monosodium hydrogen phosphate and disodium hydrogen phosphate. Monosodium hydrogen phosphate would represent the acid salt while disodium hydrogen phosphate would represent the basic. These two salts are paired in blood. The salt in a buffer pair is usually highly ionized. The other member of the pair whether it be an acid or a base is weak and, therefore, poorly ionized.

Buffer pairs in blood and body fluids are chiefly salts derived from strong bases and weak acids paired with weak acids. The acid resulting from the hydrolysis of the salt suppresses the ionization of the free acid constituting the other member of the buffer pair. The undissociated molecules of acid do not release hydrogen ions and, therefore, do not impart acidity. An acid is an acid

only when it yields hydrogen ions in an aqueous solution.

Two general rules may be applied to the action of buffers: (1) The hydrogen ion concentration in a buffered solution is proportional to the ratio of the free buffer acid and the free buffer base or

$$[H^+] = \frac{[HA]}{[BA]} \times K_1$$

In this case, H equals the concentration of hydrogen ion, HA the concentration of a weak acid, BA the concentration of salt of that acid, and K_1 the dissociation constant of the acid. (2) A given buffer is most efficient in maintaining a constant hydrogen ion concentration when the members of the buffer pairs are present in equal concentration. In the case of the buffers in blood, the acid concentration nowhere approaches equality with concentration of the salt.

BUFFERS IN BLOOD

Five buffer pairs are prominent in tissues and blood: bicarbonate-carbonic acid,

$$\frac{H_2CO_3}{NaHCO_3};$$

basic phosphate-acid phosphate,

$$\frac{NaH_2PO_4}{Na_2HPO_4};$$

basic hemoglobin-free hemoglobin,

$$\frac{HbO}{BHbO};$$

basic oxyhemoglobin-oxyhemoglobin,

$$\frac{HbO_2}{BHbO_2};$$

and proteinate-protein,

$$\frac{H \text{ protein}}{B \text{ protein}}.$$

The basic ion of the salt is indicated by the letter B which signifies any cation (K, Na, Ca or Mg) of the total base of blood or tissues. Each pair has its own optimum pH at which it is most efficient. Serum proteins are most efficient as buffers at the normal pH of blood. However, they contribute only a minor effort to the total blood buffer action. The phosphates are also most efficient at the pH of the blood. Their concentration in the blood, relatively speaking, is low so that they too add little to the entire buffer action. Bicarbonates are the most abundant of the buffers but they operate at pH below 7.0. They, therefore, are inefficient at the pH of blood and, therefore, contribute little to the buffer action until serious acidemia ensues. They may, therefore, be considered the last line of defense. The ratio of bicarbonate to carbonic acid is about 20/1 at the pH of 7.4. The bicarbonate buffer pair does not become efficient until the pH approaches 6.8.

The chief buffer in the blood is the basic hemoglobin-hemoglobin pair. Both oxyhemoglobin and reduced hemoglobin are weak acids which combine with intracellular potassium.

CARBON DIOXIDE TRANSPORT

CHLORIDE SHIFT

As arterial blood passes into the capillaries the oxygen is released and passes into the cells. Carbon dioxide diffuses from the cells into the plasma and thence into the red cell where it is converted to carbonic acid. The hydrogen ion released from the carbonic acid combines with the hemoglobinates to release free hemoglobin which is acidic and potassium ion. The bicarbonate ion becomes concentrated in the cell causing a gradient to be established between the cell and plasma. Therefore, it diffuses into the

plasma. Chloride then diffuses into the cell to replace the bicarbonate ion in order to maintain the electrical balance. This shift of anions is known as the *chloride shift* (Hamburger's phenomenon). In the lung the reverse situation is encountered. The increased oxygen tension in the cells causes oxyhemoglobin to form. This is a stronger acid than free reduced hemoglobin and releases carbonic acid from the bicarbonate ion. This passes from the cell to the blood. The hemoglobin then pairs off with the potassium and releases the chloride in the cell. The chloride is then in excess in the cell and is able to shift into plasma. The bicarbonate is present in greater concentration in the plasma since the intracellular bicarbonates have been converted to carbonic acid and have left the cell. It therefore shifts from serum into the cell where it too forms carbonic acid. In the lung carbon dioxide is then released from the resulting carbonic acid and escapes from the erythrocyte into the plasma and the alveoli. The formation of carbonic acid in the red cell in tissue capillaries from carbon dioxide and water is catalyzed by an enzyme called carbonic anhydrase. This enzyme increases the velocity of the reaction at least a thousand times. The reaction can go on without the enzyme but it does so at a very slow rate. In the lungs the carbonic anhydrase catalyzes the breakdown of carbonic acid to carbon dioxide and water.

CARRIAGE AS BICARBONATE

Carbon dioxide, therefore, is carried from tissues to the lung in plasma in the form of the bicarbonate ion. This bicarbonate ion is balanced by the cations of the plasma which are mainly sodium. The hydrogen ion, which is added to blood by formation of carbonic acid, passes into the erythrocyte which carries it in the form of reduced hemoglobin. Reduced hemoglobin is a weak, poorly ionized acid whose ionization is further suppressed by the potassium hemoglobinate normally in the cell. The membrane of the red cell is impermeable to cations normally present in plasma (sodium and calcium). Hydrogen ion is the only cation which passes in and out of the membrane easily. Bicarbonate and chloride ion concentrations in the plasma are in reverse ratio to each other.

CARBAMINO COMPOUNDS

Hemoglobin is capable of combining with carbonic acid directly by virtue of the amino groups in the protein of the hemoglobin to form a carbamino compound. This compound is a neutral, unstable substance which is readily decomposed and releases carbon dioxide as it passes through the pulmonary capillaries. Approximately 20% of the total blood carbon dioxide is carried as the carbamino compound. The combination of carbon dioxide with hemoglobin occurs rapidly and is probably complete in less than a thousandth of a second.

ROLE OF THE KIDNEY IN THE ELIMINATION OF ACIDS

Non-volatile acids, such as lactic, phosphoric, acetoacetic and so on, if added to blood, are immediately buffered by one of the aforementioned buffer pairs. They usually react with disodium hydrogen phosphate to form monosodium dihydrogen phosphate which is excreted by the kidney. The kidney, therefore, eliminates non-volatile acids as an anion combined with a cation. The lactate ion persists in blood until excreted by the

kidney or it is converted to glycogen by the liver.

The kidney attempts to conserve base. When fixed acids accumulate at a rapid rate and the loss of excessive base is imminent, the kidney forms ammonia which neutralizes the acid to form ammonium salts. These salts are excreted by the kidney. The blood and tissue base is maintained in a steady state until acid production becomes so great that this mechanism of conservation fails.

NORMAL BLOOD pH

The pH of blood remains remarkably constant even though large amounts of acids are being formed and added to blood continually. The normal serum pH ranges between 7.35 and 7.45. The pH of serum is slightly higher than that of whole blood because the cells, which are more acid, are removed. Blood pH is lowest early in the morning and increases progressively until late in the evening. This change, however, is slight varying from .01 to .05 pH units and clinically insignificant. Exercise, exertion, and other physiological factors may cause a slight increase in blood pH. Venous blood is slightly more acid than arterial blood (0 02 pH units).

BLOOD CARBON DIOXIDE CONTENT

The term total carbon dioxide content of blood refers to the amount of carbon dioxide which can be liberated from 100 ml. of whole blood collected anaerobically when treated with an acid. The quantity normally varies from 55 to 75 volumes per cent. Arterial blood contains approximately 5 volumes per cent less than venous blood. The total carbon dioxide content of whole blood is a composite of (1) the dissolved carbon dioxide, (2) the carbon dioxide present as car-

bonic acid, (3) the carbon dioxide combined with base as bicarbonate, and (4) carbon dioxide combined with protein as carbamino compound. Carbon dioxide content represents the amount of carbon dioxide present in a free or combined state at a particular moment in a vessel. Carbon dioxide content must not be confused with carbon dioxide combining power which is an entirely different concept. Combining power is a measure of the potential the plasma possesses to form bicarbonates from the base present. Combining power is determined by exposing serum to an atmosphere containing 5% carbon dioxide (the concentration of alveolar air). The serum is then treated with an acid and the volume of carbon dioxide liberated is collected and expressed in volumes per cent. The total carbon dioxide content at a given moment in volumes per cent could conceivably be, say for example, 20 volumes per cent. This is far below normal. Such a situation could develop by hyperventilation during which the carbon dioxide is removed at a more rapid rate than normal The total base during hyperventilation remains unchanged but is electrically offset by chlorides and other anions instead of bicarbonate. The combining power, therefore, remains the same and would be normal (55–60 volumes per cent). The plasma bicarbonates not only transport the carbon dioxide from cells to lung but act, together, with free carbonic acid as a buffer pair. The bicarbonate ion is present in large concentrations in plasma because it serves as the chief means of transferring carbon dioxide from the tissues to the lungs.

ACIDOSIS AND ALKALOSIS

The ratio between serum bicarbonates and free carbonic acid tends to remain

constant. A lowered serum bicarbonate level in the face of an unchanged acid content is soon followed by a decrease in blood pH because hydrogen ions are not adequately suppressed by buffering. An acidemia or *acidosis* results. An increase in bicarbonates without an increase in acid suppresses hydrogen ion and causes alkalemia or alkalosis. *Alkalosis* means an increase in the alkalinity of the blood or a decrease in the hydrogen ion-base ratio; *acidosis* refers to an increase in the acidity or a decrease of the base-acid ratio. The terms are sometimes used to indicate decreases or increases of total base. This causes confusion because base may either be increased or decreased with appreciable change in hydrogen ion concentration. The term acidosis indicates that hydrogen ions have increased and alkalosis that hydrogen ions have decreased in relation to total base and that as a result the pH has shifted. The balance between buffer base and free acid in blood and tissues is referred to as acid base balance.

pCO₂, pH AND CARBON DIOXIDE CONTENT

In studying the acid base balance of blood data concerning three factors must be supplied to provide the necessary information. These are the plasma pH, the bicarbonate ion concentration, and carbon dioxide tension. If any two of these are known, the third may be calculated by using the Henderson-Hasselbalch equation

$$\left(pH = pK_1 + \log \frac{BHCO_3}{H_2CO_3} \right).$$

The blood carbon dioxide tension, often referred to as pCO_2, is an important determination from an anesthetic point of view since it offers a clue to the efficacy of pulmonary ventilation and gaseous exchange. This may be computed from the blood pH and the total carbon dioxide content of whole blood. It is noteworthy that an error of 0.01 pH units in this computation may result in an error of 10 mm. Hg CO_2 tension. Normally the arterial pCO_2 is 40 mm. Hg; the venous is 46 mm. Hg. The alveolar pCO_2 equals that of the arterial blood. Alveolar CO_2 may be measured by determining the CO_2 tension in a sample of air taken at the end of expiration. This is referred to as *end expired CO₂*. If distribution of gases and perfusion of the alveoli are normal it closely reflects arterial pCO_2. Anything that retards passage of carbon dioxide into the alveoli would introduce an error in the results. Generally an increase in CO_2 tension indicates inadequate pulmonary ventilation. In clinical studies, the carbon dioxide combining power, often referred to as the alkali reserve, is used as an index of the state of the acid-base balance.

ACIDOSIS

The accumulation of any acid in the blood in large quantities disrupts the buffering mechanism and results in acidosis. Acids which form in the body are of two types, volatile or gaseous and non-volatile or fixed. Retention of carbon dioxide causes carbonic acid to form and be retained and results in a *gaseous* or *respiratory acidosis*. Base is retained to form more bicarbonate ion to buffer the retained carbon dioxide. Sooner or later if carbon dioxide continues to be retained the buffering mechanisms fail and the pH shifts towards the acid side of normal. Fixed acids form during metabolism. These include lactic, phosphoric and others. Normally the kidney

excretes these as monosodium acid phosphates or salts of ammonia in order to conserve base. When they form in large quantities they combine with and deplete base giving rise to metabolic acidosis. Should the base increase in proportion to the acid, so that pH does not change, the acidosis is referred to as *compensated*. Should the acid fall in proportion to the base so pH does not change the acidosis likewise is *compensated*. Should base increase and acid is retained to offset the increase so pH does not change the alkalosis is referred to as *compensated* alkalosis. Should the base increase out of proportion to acid, the pH rises and an *uncompensated* alkalosis results. Should acid increase out of proportion to base the pH falls and the acidosis is *uncompensated*.

COMPENSATION OF ACIDOSIS AND ALKALOSIS

The relationships of the carbon dioxide tension to total carbon dioxide content have been described graphically by

Van Slyke (Fig. 1.29). The abscissa represents the CO_2 tension in mm. Hg pressure and the ordinate the total CO_2 content in volumes per cent. The ratio represents the pH according to the Henderson-Hasselbalch equation. A given point on the graph represents a definite ratio between H_2CO_3 and base-bicarbonate. A line drawn from the origin (zero) through such a point represents variation of total amounts in the same ratio. Since the ratio represents pH, any straight line through the origin and a given point will represent the same pH. Van Slyke drew four such lines representing pH; one for 7.3 and one for 7.4, which represent ratios of buffer systems within normal limits and one for 7.0 and the other for 7.8 representing limits compatible with life. The lines representing the CO_2 dissociation are curved. These curved lines intersect the straight lines representing pH giving rise to nine areas. The term *compensated* was used by Van Slyke for any change in the buffer system in which pH remains normal and *un-*
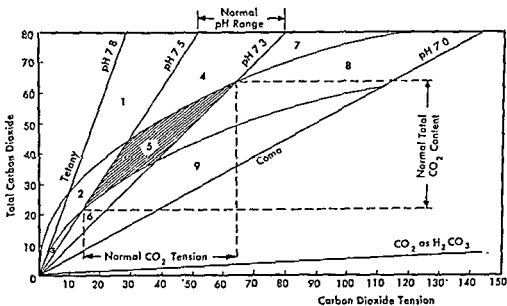
FIG. 1.29.

compensated for conditions outside this range. A line near the abscissa indicates CO_2 present as H_2CO_3. The nine areas are described in Figure 1.29.

The carbon dioxide combining power of adults ranges from 50 to 75 volumes per cent. The figure is somewhat lower for infants. A low combining power merely indicates a low reserve of alkali available to pair off with bicarbonate ion or to combine with carbonic acid. The total base in blood may be normal or even increased even though the carbon dioxide combining power is below normal because it is paired off with an anion derived from a non-volatile acid or combined with another acid. Therefore, it is not available to combine with carbon dioxide. The base is not revealed in the test even though it is present in the serum being analyzed. A deficit of base available to combine with carbon dioxide may be offset by a decrease in blood carbon dioxide tension so that no alteration in the pH occurs. A combining power below 20 volumes per cent is serious because at this level compensatory mechanisms are so deranged that a fall in pH is inevitable. Blood pH determinations are necessary for a precise appraisal of the status of the acid-base balance when combining power values are below 20 or above 80 volumes per cent.

Carbonic acid is a weak, volatile acid, which is easily converted to carbon dioxide and water. Therefore, it is eliminated via the lungs. When non-volatile acids, such as sulphuric or lactic, are infused into blood, the bicarbonates of plasma react to form sulphates, lactates and other anions and free carbonic acid. The carbon dioxide liberated from the carbonic acid in turn stimulates respiration, which in turn increases ventilation or facilitates elimination. Thus, the hydrogen ion added to the blood by the non-volatile acid is lost as the volatile acid, carbon dioxide. Thus, no acid stronger than carbonic may exist in the plasma. However, when a non-volatile acid is added to blood, the anions which form are balanced with the cations derived from the blood alkali. This base is no longer available for combination with carbon dioxide. Excessive formation of fixed acids causes renal excretion of base in an attempt to eliminate excess anions. The total base and the alkali reserve are both depleted. The combining power is decreased and acidosis results when the buffering mechanism no longer compensates for the addition of acid.

ACID-BASE BALANCE AND ANESTHESIA

The acid-base balance may be disturbed during anesthesia. All the known anesthetics and narcotics decrease the sensitivity of the respiratory center to carbon dioxide. This, in turn, causes decreases in ventilation which, as a rule, are accompanied by varying degrees of anoxia or carbon dioxide retention or both. Both are disturbing influences to the acid-base balance. The carbon dioxide retention results in respiratory acidosis; the anoxia may lead to accumulation of non-volatile acids. Besides the diminished ventilation from central depression, airway obstruction due to secretions, faulty apparatus, and other technical difficulties cause carbon dioxide retention. Metabolic disturbances may cause the release of fixed acids. These combine with and deplete the base. Impaired renal function may accompany anesthesia, which in turn interferes with the elimination of these acids which effects the composition of the blood. Disturbances in liver function may further

contribute to changes in acid-base balance, since the liver is intimately concerned with carbohydrate metabolism, which in turn is associated with release of phosphoric acids. The lactates also are converted to glycogen by the liver. The inability to convert lactates to glycogen results in their accumulation and depletion of base. Thus, it is obvious that many variables must be considered in studying the effects of anesthetics upon the acid-base balance. The failure to consider these variable factors is no doubt responsible for much of the conflicting data regarding this subject.

The bulk of the evidence indicates that some degree of respiratory acidosis may be anticipated with all general anesthesia, particularly when basal narcotic doses of non-volatile hypnotics and narcotics are used in combination with volatile anesthetics. Alveolar carbon dioxide concentrations ranging between 5.6 to 30% have been reported during general anesthesia. The hypercarbia persists in varying degrees for hours in long operations. Respiratory acidosis, once it occurs, is not quickly corrected. Farhi and Rahn have observed that sudden decreases in ventilation do not cause an abrupt rise in carbon dioxide tension. Instead, the changes in composition of alveolar gases is exponential with time. In their studies the half-way changes from one steady state to the next required approximately 4 minutes. It has been observed in cases in which alveolar tension rose to four times above normal as a result of decreased ventilation that as many as six minutes may be required to reduce the tension to normal if hyperventilation is commenced. Hyperventilation does not cause a prompt return to normal tensions. The reason for this lag is due to the fact that carbon dioxide is, relatively speaking, quite soluble in

water and is thus stored in the tissues before its accumulation becomes apparent. Carbon dioxide differs from oxygen in this respect. Alveolar oxygen tension is altered quickly in oxygen deprivation. The anoxemia produced is corrected in a matter of seconds when oxygen is supplied.

EFFECTS OF RESPIRATORY ACIDOSIS

The effects of respiratory acidosis are difficult to access. Long term effects are ill-defined. It is difficult not to conclude that the effects are not serious when one considers how frequently it develops and persists without apparent ill-effects. The effects are probably obscured by the metabolic effects of stress during operation. Sudden reversal of hypercapnia may lead to hypotension. This has been observed after cyclopropane anesthesia. However, it may occur with any drug which leads to hypercapnia. The signs of hypercapnia during anesthesia are variable and depend upon the degrees of retention of carbon dioxide and the susceptibility of the individual patient to the gas. This factor varies widely from subject to subject.

POTASSIUM AND ACIDOSIS

Electrolyte shifts have been ascribed to respiratory acidosis. During acidosis K^+ and H^+ shift from the cell and Na^+ diffuses inward. The mean plasma potassium rises as the administration of anesthesia is continued. Changes in potassium in anesthesia uncomplicated by acidosis are small, however. During respiratory acidosis the myocardium takes up K^+ which it releases later when the acidosis is corrected. The extracellular sodium, potassium and bicarbonate ions increase. Sodium chloride and bicarbonate ions increase in the red blood cell. Carbon dioxide excess stimulates

the sympathico-adrenal system. The K^+ is therefore released from the liver by (1) the sympathico-adrenal activation and its resultant glycogenolysis also and (2) by the elevation of blood pH which causes a migration of K^+ from the cell to blood. The K^+ excess has been implicated in sudden cardiac arrest. The disturbance in carbohydrate metabolism which has been reported during respiratory acidosis are similar to those occurring during ether anesthesia.

METABOLIC ACIDOSIS AND ANESTHESIA

Much data concerning metabolic acidosis during anesthesia are available. Data on acidosis during ether anesthesia are conflicting, however, the bulk of the evidence indicates that metabolic acidosis accompanies ether anesthesia. A definite and pronounced reduction in serum and blood bicarbonates accompanies both ether and chloroform anesthesia in both man and experimental animals. The pH is lowered. The severity of the acidosis varies with the depth and duration of anesthesia. An increase in hydrogen ion concentration and carbon dioxide tension occurs which suggests that bicarbonate is displaced from combination with base by non-volatile acids. The biochemical changes appear within the first few minutes of anesthesia and persist for varying periods of time after termination of anesthesia. The effects are more pronounced with chloroform. In operated man 24 hours or more may be necessary for the combining power to return to pre-operative levels following ether anesthesia. Bourne and his associates suggested the accumulation of organic phosphate, presumably the result of disturbed carbohydrate metabolism, was the cause of the reduced combining power. Ronzoni and Root noted increases in lactate and pyruvate and a lowering of serum bicarbonate during ether anesthesia. Root and co-workers found no significant changes in serum sodium and serum chloride in dogs anesthetized with ether for one hour. The carbon dioxide capacity was reduced (4.8 m.Eq. to 6.6 m.Eq.) and serum lactate was increased. The increase in lactate was in proportion to the lowering of bicarbonate. The impaired carbohydrate metabolism is associated with the release of epinephrine and norepinephrine which occurs during ether anesthesia. The metabolic acidosis of ether anesthesia is transient and of no serious consequence ordinarily. An existing acidosis of the type found in diabetes, renal failure, dehydration or in chronic respiratory acidotic states associated with pulmonary disease might be aggravated by such a change.

NITROUS OXIDE AND ETHYLENE

A slight change in carbon dioxide combining power and serum pH is noted during *nitrous oxide* and ethylene anesthesia, if it is uncomplicated by anoxemia. Anesthesia, of course, is in no way as profound as it is with ether or chloroform.

CYCLOPROPANE

Reports on the effects of cyclopropane vary. Seevers, Fay, Neff and co-workers reported slight changes in plasma pH, an increase in carbon dioxide tension and an elevation of serum bicarbonate in man. These workers believe acidosis during cyclopropane is of the "gaseous" type and is due to rebreathing of carbon dioxide from the "dead spaces" of the anesthesia apparatus.

The changes in acid-base balance during cyclopropane anesthesia are largely those resulting from an increase in car-

bon dioxide tension due to diminished or inadequate ventilation.

NON-VOLATILE DRUGS

During basal narcosis with tribromethanol a reduction of serum bicarbonate and an increase of hydrogen ion concentration is noted. Similar changes accompany paraldehyde, morphine, and barbiturate anesthesia. The severity of the acidosis accompanying the use of the latter, non-volatile drugs varies with the degree of narcosis present. Amytal, pentobarbital, and secobarbital cause a decrease of serum pH when used in amounts sufficient to produce deep hypnosis or surgical anesthesia. Changes using thiopental are slight unless respiratory depression is severe. Morphine anesthesia (Rakieten and others) produces a "gaseous" acidosis in dogs. Serum pH is lowered, carbon dioxide tension is elevated, and carbon dioxide combining power is reduced. Serum total base, chlorides, and fixed acids (lactic) do not change. If, during anesthesia using these non-volatile drugs, the depression of respiration is slight or only sedative doses are used, the results are inconsistent and acidosis, on the whole, is slight or absent.

SPINAL AND LOCAL ANESTHESIA

Uncomplicated spinal anesthesia is followed by slight or no changes in acid-base balance. If anesthesia extends to the upper thoracic dermatomes and is accompanied by circulatory and respiratory depression, anoxemia or carbon dioxide retention, disturbances in acid-base balance do occur. Local and nerve block anesthesia is accompanied by insignificant or no change of acid-base balance.

ANOXIA

Anoxia, irrespective of the cause, profoundly upsets acid-base balance. Fixed acids, particularly lactic, are liberated. A fall in serum pH, a decrease in serum bicarbonate and an increase in lactate are the changes usually observed. Presumably these changes are due to disturbances in carbohydrate metabolism since lactic acid accumulates because oxygen necessary for conversion to glycogen is not available. The acid displaces carbonic acid from the blood and lowers serum bicarbonate and carbon dioxide combining power. Asphyxia is accompanied by both anoxia and a retention of carbon dioxide. It, therefore, further increases the acidosis by superimposing a metabolic one or a respiratory one.

Recently a new therapeutic agent known as THAM (2-hydroxy methyl 2 amino, 1,3 propandiol) has been introduced as a therapeutic agent to correct respiratory acidosis. The agent combines with carbon dioxide and is excreted into the urine.

HYPOTHERMIA

At lower temperatures, the solubility of carbon dioxide in plasma is increased. It was thought for some time that this would lead to acidosis if steps were not taken to reduce the tension in blood. However, other changes occur simultaneously with temperature reduction. Additional base becomes available for combination with carbon dioxide. Presumably most of this comes from decreased ionization of proteins at the lower temperature. As a result the pCO_2–pH relationships differ little at 37°C. and 25°C.

Errors in studies of acid base balance have been introduced by failure to make appropriate temperature corrections in methods of determining carbon dioxide tensions and pH. The decreasing of vapor pressure of water with decreasing temperatures must be taken into account

in computations. The change in the pH for CO_2 is +0.005 units per degree reduction in temperature. Blood pH measured at the temperature of the glass electrode used in the determination may be converted to body temperature by considering the fact that its pH rises 0.0147 units per °C. decrease below 37°C. One additional factor to be considered is that the dissociation constant of water decreases with temperature. The point of the neutrality on the pH scale is 7.00 at 25°C. and 6.80 at 37°C. and 7.5 at 0°C. Unless metabolic acidosis develops it appears unlikely that a marked reduction in carbon dioxide tension during anesthesia is of such dire importance.

KETONE BODY FORMATION AND ACIDOSIS

Ketone body formation accompanies ether, chloroform, and other types of anesthesia. However, these appear after the anesthesia has been in progress for some time. They add to the acidosis in a small way but are not responsible for it.

CONVULSIONS DURING ANESTHESIA AND ACID-BASE BALANCE

One group of complications of clinical anesthesia which may be linked to changes in acid-base balance and acidosis are the so-called "ether convulsions." Many papers have been written about this subject but little light has been shed on its etiology. There is some evidence that acidosis may play a role. Data by Seevers, Cassels, and Becker suggest there are several causative agents and these acting together produce the cerebral irritability required for the muscle spasms and convulsions. In experiments on rats and dogs convulsions or muscle twitchings were observed most frequently when pyrexia, carbon dioxide excess (10% or more inhaled) and ether

anesthesia were present all at the same time. The data support the contention that pyrexia and factors which induce a "metabolic" acidosis in the anesthetized subject increase irritability of the nervous system and that a "gaseous" or respiratory acidosis superimposed upon the "metabolic" acidosis acts as the precipitating agent which initiates the convulsion. The fact that convulsions occur, not only during ether anesthesia but also with other agents, supports this view. Thus, carbon dioxide excess may be a contributory factor, if it is not the dominant one, in causing this distressing syndrome.

HYPERVENTILATION AND ACID-BASE BALANCE

Seevers and Waters and their associates completed exhaustive studies on the effect of hyperventilation on anesthetized animals and man. Human subjects anesthetized with ether, cyclopropane, avertin, amytal, and morphine-scopolamine were hyperventilated for periods of ten to twenty minutes. During this time a marked alkalosis occurred characterized by a rise in serum pH (as much as 0.31 units), a lowering of carbon dioxide tension, and a decrease of carbon dioxide content in blood. Tetany was absent during narcosis with ether and cyclopropane but not with nitrous oxide, ethylene and other mild agents. The peripheral circulatory failure believed to result from acapnia by Henderson was notably absent.

Vigorous over-ventilation of a conscious person may so lower the plasma carbon dioxide that the pH rises excessively. Under these circumstances unconsciousness results with electroencephalographic changes. It has been suggested that respiratory alkalosis during anesthesia may initiate cerebral vasocon-

striction and produce cerebral damage from the resulting anoxia. Most of the data available indicates that the over-ventilation must be severe in the order of 100–150 liters per minute for this to occur. The conventional method of pro-ducing hyperventilation during anesthe-sia seldom produces ventilation exceed-ing 20 liters per minute. It is unlikely that this degree of hyperventilation is a serious hazard during anesthesia. Clini-cal experience bears this out.

Effects of Anesthesia Upon Composition of Body Fluids. Organic Constituents

BLOOD NITROGEN

THE NITROGEN-CONTAINING CONSTITUENTS of body fluids may be divided into two categories: *protein* and *non-protein*. Non-protein nitrogen (N.P.N., B.U.N.) forms a small fraction of the total nitrogen of blood. The concentration of non-protein nitrogen in blood may be an important index of the metabolic processes going on and efficiency of excretory mechanisms of the body. The important substances composing the non-protein nitrogen fraction of blood are *urea, uric acid, creatine, creatinine, amino acids, glutathione, ammonia,* and *guanidine*. The concentrations of urea, uric acid, and creatinine in blood are of clinical significance since they are elevated during renal insufficiency, dehydration and various metabolic disturbances. The normal fasting non-protein nitrogen ranges from 25 mgm. to 40 mgm. per 100 ml. Approximately 12 mgm., or almost 50% is derived from the urea fraction, 1% from uric acid, 0.6% from amino acids, 1% from creatinine and ½% from creatine. The remainder probably comes from various non-protein constituents found in erythrocytes. When non-protein nitrogen blood levels rise during renal insufficiency uric acid, as a rule, increases first, urea next, and ultimately creatinine. Any pathological proc-

ess which causes an individual constituent to increase, obviously, raises the total non-protein nitrogen in the blood. Deviations from normal levels suggest, but do not necessarily establish, the presence of (1) renal insufficiency, (2) blood volume changes or 3) metabolic disturbances. The source and variations in concentration of each component in the blood non-protein nitrogen fraction are best considered individually.

UREA

Urea is the diamide of carbonic acid. Urea is a neutral substance but the presence of two amino groups permit it to form salts with acids. Urea is formed chiefly in the liver as the main nitrogenous end product of protein metabolism. Blood urea is distributed almost equally between the cells and plasma. The blood concentration varies from 5 mgm. to 23 mgm., expressed as nitrogen, per 100 ml. of blood. The range for fasting individuals varies between 10 mgm. to 15 mgm., expressed in terms of elementary nitrogen. Urea is diffusible and, because of this, is found in other body fluids besides blood. It is found in ascitic fluid, saliva, and cerebrospinal fluid in concentrations slightly less than that of blood. Although under normal circum-

stances almost 50% of the non-protein nitrogen of blood is derived from urea when the non-protein nitrogen is increased, the proportion of urea nitrogen may be as high as 85% to 90% of the total. Consequently, in clinical studies, urea determinations yield useful data. The blood urea nitrogen (B.U.N.) is used as an index of the total non-protein nitrogen in many laboratories since it is easier to determine. Blood urea increases after ingestion of large quantities of proteins and decreases somewhat after ingestion of carbohydrates. Dehydration causes a slight increase while diuresis causes slight decrease of blood levels. Slight increases also occur in starvation, probably due to dehydration. In pregnancy, a decrease may occur. Age does not affect the blood urea level, as a rule. Blood urea falls in severe liver disease while amino acids show an increase due to the failure of the liver to deaminize amino acids.

Concentrated urea is injected intravenously to reduce organ volume, particularly that of the brain. The urea increases the total osmolarity of the blood and fluid is withdrawn from the interstitial and intracellular spaces. The urea produces a diuresis.

Changes During Anesthesia

Blood urea levels may rise during anesthesia. This results secondarily from the antidiuretic effect and changes in renal blood flow caused by anesthesia or a compensatory polyuria may follow recovery with a return of the blood levels to normal (see Chap. 33).

Uric Acid

Uric acid is derived from two purines, adenine and guanine. These are found in plant and animal nucleic acids. Both purines, aided by enzymes, (deaminases and oxidases) are converted to hypoxan-

thine (adenine), xanthine (guanine) and then to uric acid. Uric acid is a white crystalline substance, sparingly soluble in water. Blood uric acid is present in the form of urates of potassium, sodium and ammonium. Urates of alkali metals are more soluble in water than those of the free acid. The uric acid molecule has three hydroxyl groups which react with cations to form a tribasic salt. However, only the monobasic salt forms at the pH of blood. Some uric acid combines with organic radicals. This exists in the form of "*bound*" *uric acid*. The bound form is deposited in tissues in pathological conditions such as gout. The plasma concentration of uric acid is higher than that of the cells. Most of the uric acid is derived from exogenous sources obtained from foods containing nucleic acids. Some is obtained from the breakdown of tissue cell nuclei. The average blood values of normal individuals varies between 3 and 5 mgm. per 100 ml. of whole blood. Ingestion of foods containing large amounts of proteins causes little change in blood uric acid levels. The administration of large amounts of vitamin C causes an elevation in blood uric acid levels. Elevated blood uric acid levels result from renal insufficiency, disturbances of purine metabolism, or excessive destruction of nucleoprotein. Plasma levels are increased during severe muscular exercise, during starvation (probably due to the destruction of the tissues), in nephritis, gout, eclampsia, polycythemia vera, leukemia, and multiple myeloma.

Amino Acids

Amino acids are normal constituents of blood. They form from the hydrolysis of proteins during the digestion of proteins in the gastrointestinal tract and from catabolism of body tissues. At least

25 amino acids are recognized in proteins of mammals. Amino acids cannot be stored in the body when taken in excess of body needs. Therefore, those which the body does not utilize in synthesis of protein are deaminized by the liver. The amino group combines with carbonic acid through a series of complex reactions aided by enzymes to form urea. The rest of the molecule is converted to carbohydrate or fat, depending upon the type of amino acid involved and the carbohydrate or fat stored. The concentration of amino acids in whole blood varies between 5 mgm. and 8 mgm. per 100 ml. The concentration in red cells is about three to four times that of plasma. The ingestion of large quantities of proteins causes an elevation of blood amino acids. This is most striking particularly in the blood from the portal vein. Fasting, pregnancy, age and sex cause few alterations in blood amino acids. Insulin and epinephrine cause the blood level to fall. In most forms of acute hepatitis, a marked increase of blood amino acids accompanies the disease. Slight elevations also occur in nephritis, diabetes, hyperthyroidism, cardiac failure, cancer, fever, and leukemia. Hepatitis due to chloroform and other halogenated hydrocarbons is accompanied by an increase in the plasma and urinary amino acids. Cystinuria is a metabolic disease characterized by excretion of cystine in the urine. The level of cystine in blood is elevated and the amino acid appears consistently in the urine.

Determinations of blood amino acids are of little clinical significance as far as anesthesia is concerned with the exception of hepatitis caused by chloroform and other halogenated compounds, in which case it has some diagnostic and prognostic value. The amino acids contribute to the non-protein fraction of nitrogen analysis of blood.

CREATINE AND CREATININE

Creatine is a normal constituent of muscle and nervous tissue. Creatinine is a waste product. Approximately 98% of the creatine in the body is found in the muscles and 1.5% in the nervous tissues. Skeletal and cardiac muscle are richer than smooth muscle. Four-fifths of the creatine is combined with phosphoric acid as phosphocreatine. Phosphocreatine supplies the phosphate for the conversion of adenylic acid and adenosine triphosphate, the breakdown of which liberates the energy necessary for the work of muscular contraction. Creatine is synthesized in the muscles from amino acids. The creatine obtained from dietary sources presumably is not utilized. Synthesis is not dependent upon the liver.

Creatine and creatinine are colorless, odorless, and tasteless, water soluble, nitrogen-containing organic substances. Creatine is *methyl-guanido acetic acid*. Creatinine is the anhydride of creatine *and forms from creatine by the loss of* one molecule of water.

$$
\begin{array}{c} NH_2 \\ | \\ C{=}NH \\ | \\ CH_3{-}N{-}CH_2COOH \end{array}
\qquad
\begin{array}{c} NH \\ \| \\ C \\ HN \diagup \diagdown N{-}CH_3 \\ | \qquad | \\ OC{-}\!-\!-\!CH_2 \end{array}
$$
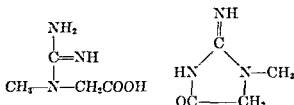
Creatinine is not converted to creatine in the body. Only traces of creatine are excreted into the urine. Creatine output into the urine is increased only when the liberation in tissues is increased and exceeds the ability of the body to convert it to creatine. Creatinine is one of the means of disposal of nitrogen by the organisms just as urea is a product of deamination of amino acids.

Most of the creatine is in the cells. Little is found in the plasma. The normal concentration of creatine in whole blood varies between 2.5 mgm. and 5 mgm. per 100 ml., the average value usually being about 3 mgm. Exercise and diet change the blood creatine level very little. Little change is observed in most pathological states.

The blood creatinine level also remains remarkably constant. It ranges between 1 mgm. and 2 mgm. per 100 ml. of blood. Age, exercise, diet, and other factors affect the blood concentration very little. Creatinine is evenly distributed between the red cells and plasma. Blood creatinine levels are elevated in all types of renal insufficiency, in wasting diseases of muscles, such as muscular dystrophies and after destruction of muscle tissues. Blood creatinine exceeding 2 mgm. per 100 ml. are considered to be above normal. A value of 5 mgm. per 100 ml. indicates severe renal insufficiency and is considered of grave prognostic significance. Elevation of blood creatinine levels occurs after the urea has increased usually. Creatinine is retained in blood in the various nephritides, obstructions of the urinary tract, intestinal obstruction, toxemias, pneumonia, and dehydration. Creatine is not a waste product of metabolism. Blood levels change very little in pathological states except in total renal shutdown when a rise in blood concentration occurs. Little information is available on the metabolism and excretion of creatine during anesthesia. There is, however, little reason to suspect any deviations of blood level from normal.

AMMONIA

The amount of ammonia formed normally in the body is small in comparison to the total nitrogen excreted as urea. In acidosis, however, ammonia is formed by the renal tubule to neutralize acid and conserve base. This ammonia is derived from amino acids and not as one would suspect from the urea passing through the kidney. Presumably the important source is glutamine. This is aided by the enzyme glutaminase, which catalyzes the reaction. The blood concentration, however, is changed little under these circumstances. The blood leaving the kidney (venous) contains slightly more ammonia than that entering it. Under normal conditions 30–50 m.Eq. of H^+ are eliminated per day combined with ammonia formed by the kidney.

Considerable quantities of ammonia are formed in the large intestine as a product of putrefactive activity on nitrogenous substances by the intestinal bacteria. Normally the ammonia is absorbed but it is converted to urea by the liver. In hepatic disease the conversion does not occur and toxic levels result which are believed to be the genesis of the so-called hepatic coma. The effect of ammonia on the nervous system is not clearly understood.

The usual concentration of ammonia in whole blood is less than 0.1 mgm. per 100 ml. In hepatic coma it has been known to rise. The blood ammonia is remarkably constant in kidney diseases and in toxemia of pregnancy. The blood level, however, is very little changed even in these circumstances. Blood ammonia levels are increased during ether anesthesia, but data on this subject are meager.

GUANIDINE BASES

Guanidine is another constituent of the non-protein nitrogen fraction of blood. The chemistry of guanidine and

its significance in blood are not understood exactly. In normal blood, the concentration of guanidine is believed to be approximately 1.5 mgm. to 2.30 mgm. A number of different derivatives are believed to exist but calculations of blood levels are usually based upon the assumption that the substance is methyl guanidine. *The concentration in the plasma is approximately half that of the cell.* Guanidine levels may be increased in uremia, in epilepsy, and severe liver diseases. Rises parallel increases of urea and creatinine in blood when renal insufficiency is present. The exact role of guanidine has not been established from a clinical standpoint. There is no known relationship to anesthesia of significance. It might be noted, though, *the bases are increased in blood in convulsive states,* such as epilepsy.

CHANGES IN NON-PROTEIN NITROGEN DURING ANESTHESIA

Obviously, since the non-protein nitrogen derivatives are metabolic by-products which are eliminated by the kidney their concentration in blood is bound to vary with metabolic activity, cardiovascular status, state of hydration and so on. Studies of their variation during anesthesia can be of significance only if parallel studies are made on urine formation, interstitial fluid composition, blood volume, liver function and the like. A good deal of the available data consists of isolated determinations of blood levels which are not correlated with any of the aforementioned factors. Generally, most of the data indicates that significant changes in blood non-protein nitrogen due to anesthesia are uncommon. Slight elevations may occur during anesthesia due to the antidiuresis which accompanies anesthesia with

many agents and from changes in blood volume. A restoration to normal blood levels usually occurs after recovery from anesthesia. Blood urea levels increase during ether anesthesia. Two factors may be involved: (1) a temporary reduction in urine formation, and (2) a possible increased production of urea by the liver. Although the function of the liver is decreased by some anesthetics, the formation of urea is not impaired. Bollman has shown that animals manifesting extensive hepatic lesions form more urea than is normally expected under anesthesia. This may be explained by the fact that more protein is used during anesthesia due to the deranged carbohydrate metabolism. Blood urea increases during *chloroform* anesthesia not accompanied by hepatitis, and during *avertin-nitrous oxide anesthesia.* Changes due to nitrous oxide, ethylene, and cyclopropane are slight and usually negligible.

NITROGEN METABOLISM

Nitrogen metabolism is disturbed when hepatitis develops as a result of anesthesia with chloroform and other halogenated hydrocarbon anesthetics. The urea-forming capacity of the liver is decreased under these circumstances. Blood non-protein nitrogen rises as a result of a decreased urinary output, increased blood ammonia and a rise in alpha amino acid nitrogen since the liver no longer can deaminize amino acids. Purines are not increased as a rule. An *increase in blood uric acid has been observed in dogs,* however, during cyclopropane anesthesia, the significance of which is not explained except that perhaps it indicates deranged function of the liver.

PLASMA PROTEINS

Blood proteins are of utmost interest from an anesthetic standpoint, since they are intimately concerned with fluid balance, acid base balance, binding with drugs, blood clotting and so on. Blood proteins are distributed both in the erythrocytes and plasma. *Plasma proteins* are independent, separate, and chemically different from those in cells. Plasma proteins are a complex mixture of simple, mixed and conjugated proteins. They comprise the major part of the solids of the blood. Three separate groups of plasma proteins are recognized: *albumin, globulin,* and *fibrinogen.* Plasma proteins are identified according to solubility, ease of precipitation by electrolytes, study of molecular weight, and migration in electrical fields. The migration of charged particles in an electrolytic solution when an electric current is passed through the solution is called *electrophoresis.* Various protein components in a mixture migrate at varying rates in such solutions because they have different surface charges. The protein can thus be separated into different types by the layering of individual components which occurs. The albumin molecules which are smaller and most highly charged migrate most rapidly. Six distinct boundaries have been identified in human plasma. In the order of decreasing mobility are albumin, (alpha 1 and alpha 2) alpha globulin, beta globulin, fibrinogen and gamma globulin. Similar patterns have been obtained by paper electrophoresis. Other methods of study of proteins besides electrophoresis are available such as centrifugation, alcohol precipitation and immunological analysis. These reveal individual entities in a given component of an electrophoretic pattern.

GLOBULINS

The globulin fraction of proteins is a very complex mixture. This fraction is precipitated by dializing plasma with water or, by the addition of 22% sodium sulphate, or half-saturated ammonium sulphate. The more important components of the globulin fraction are the mucoproteins, the lipoproteins, metal binding fraction and the gamma globulins.

ALBUMIN

The albumin fraction is separated from plasma after the globulin is precipitated. The albumin fraction is not precipitated by half-saturated ammonium sulphate. The molecular weight of the albumin fraction is much less than that of globulin and is believed to be approximately 69,000. The albumin fraction is not absolutely homogenous. One component, however, accounts for ⅔ of the total. This fraction, called mercaptalbumin, contains one free SH group per molecule.

FIBRINOGEN

Fibrinogen is the precursor of fibrin and is concerned with coagulation of blood. Through the action of thrombin, the soluble fibrinogen is converted to insoluble fibrin. Fibrinogen is precipitated from the blood plasma by 2% calcium chloride solution or fourth-saturated ammonium sulphate. Fibrinogen has a large asymmetric molecule which is elongated. The molecular weight is between 350,000 and 450,000. Normally it constitutes 4–6% of the total weight of the protein. Fibrinogen is elaborated in the liver. Afibrinogenemia is a hereditary disease characterized by the absence, or near absence, of fibrinogen. Fibrinogen may also be depleted by the

formation of lysins in blood due to protein destroying syndromes. Purified human fibrinogen is available for treatment of these depleted states.

SITE OF FORMATION OF PROTEINS

Generally speaking, the term *serum protein* indicates the combination of albumin and globulin fractions while *plasma protein* indicates all three. Proteins are formed almost totally, by the liver. Fibrinogen and prothrombin are formed entirely by the liver. The reticuloendothelial system participates in the formation of antibodies—in other words the gamma globulins. Storage of proteins, while confined to a number of tissues, seems to be a function of the liver, also.

FUNCTIONS OF PROTEINS

Plasma proteins perform at least five functions: The first, and a very important function, is to *maintain the fluid balance* by virtue of the osmotic pressure which they exert. This tends to prevent transudation of fluid from vascular bed to tissue spaces. Albumin, because its molecule is smaller, may be lost through the endothelium of the blood vessels more easily than globulin. The osmotic pressure of albumin is approximately four times that of serum globulin so that when albumin is lost or is not formed, edema of the tissue results due to transudation of fluid from the vascular to tissue spaces. The loss of these proteins not only lowers the osmotic pressure relationships, but also disturbs equilibrium of electrolytes on either side of the cell membranes (Chap. 1). A migration of electrolytes also causes a shift of water (Donnan effect). A second function of proteins is *buffering*. Plasma proteins are amphoteric and can combine with either acids or bases. When they act as

an acid they combine with sodium, thus, making a buffer pair. Approximately 16 m.Eq. of sodium are combined with protein anions. Proteinate buffer pairs contribute about 4% to the total buffer action of blood. The third important function of protein is *nutritional*. Serum albumin is a source of protein in hypoproteinemic patients. Circulating plasma protein is not static but constantly interchanges with a labile tissue reserve. The fourth is maintenance of the *clotting mechanism.*. This is mainly a function of fibrinogen. The fifth function concerns the *mobility of red cells*. Mobility is influenced by changes in the concentration of the plasma proteins, particularly in the fibrinogen fraction. Decreases in fibrinogen cause an *increase in rate of sedimentation of erythrocytes*. Other functions of protein include transport of lipids, fat soluble vitamins, steroid hormones, drugs and possibly carbohydrates.

PLASMA CONCENTRATIONS

The *concentration of protein* in plasma varies. Although the exact concentration is not agreed upon, it is believed the total protein ranges from 6.5 grams to 8.5 grams per 100 ml. of plasma, averaging 7.5 grams. Of this, albumin is from 3.8 grams to 5.8 grams and globulin, 2.0 grams to 4 grams per 100 ml. Fibrinogen is present in amounts ranging between 0.20 and 0.4 grams per 100 ml. of plasma. Thus, the *ratio of albumin to globulin* is about 2 to 1.4. This ratio is important because changes may disturb the osmotic pressure and fluid balance between the blood and tissues. The total colloid osmotic pressure of capillary blood is approximately 28 mm. Hg pressure. Edema results when the pres-

sure falls to 18 mm. Hg or less.

Levels of plasma proteins vary under certain physiological and pathological conditions. Normally, the concentration in infants is less than in adults. A decrease in the albumin fraction may occur during pregnancy. Diets rich in protein increase plasma proteins little if at all. Dehydration may cause an increase due to hemoconcentration. High temperatures tend to cause an elevation due to an increased loss of fluid. On the other hand, if the fluid is replaced, a slight fall results due to hydremia. Excessive muscular exercise causes a slight increase in total protein of blood. Diuretics may cause an increase in concentration due to change in fluid volume.

Hypoproteinemia may be due to inadequate protein intake, excessive protein loss, or failure of protein synthesis. Plasma protein levels are lowered in severe malnutrition, liver disease, and in diseases accompanied by proteinuria, such as nephritis. The deficiency of protein is usually in the albumin fraction. Dehydration, certain diseases, such as multiple myeloma, typhoid fever, and pneumonia are accompanied by increases of total serum protein. The increase is usually in the globulin fraction. Such increases reverse the ratio also. Liver disease is accompanied by lowering the fibrinogen as well as albumin fraction. It is noteworthy that although the total protein content itself may remain constant, the albumin-globulin ratio may shift and cause physiological disturbances. The fibrinogen concentration is lowered in pernicious anemia, hemorrhage, and hemolytic jaundice.

RELATIONSHIP TO ANESTHESIA

From a surgical and anesthetic standpoint, plasma proteins are important because they reflect to a certain extent the state of nutrition of the subject. Also they are intimately concerned with liver function, blood-clotting mechanisms, wound healing, and fluid balance and reflect the status of these. The relationship between the liver and proteins is most important from the standpoint of anesthesia. Data on the effects of anesthesia on serum proteins are meager. Whatever changes occur are secondary to others caused elsewhere in the body such as fluid loss, dehydration and other factors. Stewart and Rourke, in studies of plasma volume, reported no change in plasma protein in man during *ether* anesthesia. Anesthesia with other agents seems to follow similar patterns. A decrease in fibrinogen occurs after *chloroform* anesthesia if followed by hepatitis. A decrease in sedimentation rate of erythrocytes follows chloroform anesthesia, probably due to the decrease of fibrinogen. Anesthesia with *amytal* and other *barbiturates* is also accompanied by a decrease in sedimentation rate. Possibly the factor of dilution may influence the fibrinogen concentration since hemodilution occurs with these agents. Apparently no gross deviation of globulin or albumin fractions occurs. Obviously, variations in protein content are bound to occur with changes in blood volume.

PROTEIN BINDING OF DRUGS

One aspect of serum proteins is the binding effect with non-volatile anesthetics. Procaine, thiopental, the muscle relaxants and other drugs are bound with protein. The protein bound fraction of the drug is inactive. The combination of a drug with body proteins may form antigenic substances which, in due time, are concerned with allergic reactions on subsequent exposures to these drugs. Volatile (inert) drugs do not

appear to participate in this phenomenon because their binding forces are weak. No effect of anesthesia on antigen antibody responses has been demonstrated as yet.

CLOTTING OF BLOOD

The clotting of blood is an important protective mechanism of the body. Naturally, it is of profound interest in surgery and anesthesia. Coagulation of the blood is a complex phenomenon the successful completion of which depends upon the presence of various activators and inhibitors, liver function, electrolyte balance, blood flow and many other not completely understood factors.

MECHANISM OF CLOTTING

A number of explanations for the mechanism of clotting of blood have been offered but no universally accepted process is agreed upon. Three significant steps are involved in the clotting process. The end result is that fibrinogen, which is a soluble protein, is converted to strands of insoluble fibrin in which the erythrocytes become enmeshed. The fibrin forms first as long needles and later becomes a mesh of fibres which trap the cellular elements of the blood to form the clot. Fibrinogen is converted to fibrin by *thrombin*. Thrombin is formed from *prothrombin* which, like fibrinogen, exists in a fluid state and is non-reactive until the proper conditions are present to activate it. Prothrombin is converted to thrombin by thromboplastin. A number of substances possess thromboplastic activity. These are contributed by the plasma, the platelets and the tissues. Four plasma thromboplastic elements have been described, referred to as A,B,C, and D. Deficiencies of any of these results in hemophiloid states.

Deficiencies in A type give rise to classical hemophilia. The platelet thromboplastic factor is liberated upon disintegration of the platelets. Tissue thromboplastin precursors are supplied from outside the circulation. They initiate clotting.

Prothrombin exists as an active and an inactive form. The inactive form is converted to the active by the catalytic action of accelerin and by thrombin. Active prothrombin is converted to thrombin under the influence of thromboplastin. This reaction is accelerated by calcium ions, an accelerator from platelets and several types of prothrombin accelerators.

The fibrinogen loses one or more peptides under the influence of thrombin. Activated fibrinogen first forms. The fibrin is a much larger molecule than the original fibrinogen. Prothrombin is formed exclusively by the liver. A deficiency of prothrombin results when extensive liver damage is present giving rise to clotting disturbances. *Vitamin K* is necessary for the production of thrombin. Bile is necessary for its absorption from the bowel. Deficiency of Vitamin K results in deficiency of prothrombin. Dihydroxy coumarin (Dicoumarol) antagonizes Vitamin K and produces hypoprothrombinemia.

INHIBITION OF CLOTTING

Prothrombin activation and conversion is inhibited by heparin and anti-thromboplastin. Heparin occurs on the liver and lung. It is water soluble and potent. It is used to inhibit coagulation. Heparin may be antagonized by protamine and toluidine blue. Blood fails to clot if calcium ion is absent in the plasma. Citrates and oxalates prevent clotting by precipitating calcium or converting it to the unionized form.

EFFECTS OF ANESTHESIA ON CLOTTING

Bleeding time and clotting time are not significantly changed during anesthesia with conventional drugs. It must be realized that studies on clotting are essentially observations of blood in vitro and that in vivo behavior may be quite different. During *nitrous oxide* anesthesia in dogs there is a slight increase in coagulation time. The bleeding and coagulation time in newborn infants delivered from mothers anesthetized by nitrous oxide is prolonged about one to two minutes. A shortening of coagulation time is observed after *ether* anesthesia in dogs. In man there is no significant change. Coagulation time is slightly prolonged in dogs during *chloroform* anesthesia. During *ethylene* anesthesia coagulation time is shortened but in the newborn it is prolonged. No significant change in coagulation time has been observed during *cyclopropane* anesthesia. The alleged increased bleeding is due to "ooze" resulting from vasodilatation and not to clotting. *Barbiturates* and thiobarbiturates apparently do not appreciably alter coagulation time. *Carbon dioxide* administered in concentrations which produce anesthesia (30%) shortens the coagulation time in dogs considerably. No significant changes have been reported with halothane, trichlorethylene, vinyl ethyl ether, thiopental, or the muscle relaxants. Although coagulation time is altered to a slight extent, one way or the other, clinically these aforementioned findings are of no practical significance. Increased bleeding or "ooze" during anesthesia must not be confused with defects in coagulation. Increased peripheral blood flow, resulting from vasodilatation or increased capillary blood pressure may be responsible for the oozing.

CARBOHYDRATES

HEXOSES AND GLYCOGEN

Three principal monosaccharides utilized by the cells are glucose, galactose and fructose. The sugar in the blood is glucose. The *glucose* in circulating blood is derived from three sources (1) the liver since this organ stores carbohydrates as *glycogen*, (2) glucose obtained by digestion of carbohydrates in the intestine and (3) glycogenic compounds, such as amino acids, glycerol and compounds formed from the metabolic breakdown of glucose, such as lactic, fumaric, succinic acid, etc. The storage of glycogen and the conversion of glucose to lipid (lipogenesis) is influenced by the action of *insulin*, the internal secretion of the *islets of Langerhans* of the pancreas. The miscellaneous carbohydrates ingested in the digestive tract are hydrolyzed to hexoses which in turn are converted to glucose by the liver and stored as glycogen. Glycogen is discussed later on in this chapter.

EFFECT OF HORMONES ON
BLOOD SUGAR

The blood sugar level is controlled by several *hormones*, most important of which is insulin. Insulin promotes a reduction in blood sugar. Hormones from the adrenal, thyroid and pituitary also play a role (Chap. 35). The adrenal gland elaborates a number of hormones which influence carbohydrate metabolism. Steroids with oxygen on position 11 stimulate gluconeogenesis. The release of epinephrine from the adrenal gland and norepinephrine from the adrenergic receptors mobilizes liver glycogen and elevates blood sugar. The adrenal hormones are insulin antagonists. Glycogenolysis does not occur if the liver is

depleted of glycogen. The anterior pituitary also elaborates hormones which tend to increase the blood glucose by inhibiting the action of insulin. The hormones which act in this manner are the pituitary growth hormone, corticotropin (ACTH) and a diabetogenic principle. The thyroid gland affects carbohydrate metabolism. Hypothyroidism is accompanied by a hypoglycemia; and hyperthyroidism by hyperglycemia. The pituitary gland may be the true regulator of carbohydrate metabolism by acting as a master gland which controls the other endocrine organs. As a rule, hypofunction of a gland of internal secretion tends to cause hypoglycemia, and hyperfunction a tendency towards hyperglycemia. The one exception is in the case of pituitary hypofunction in which a hyperglycemia results. Rapid elevation of blood sugar in emergency states is dependent upon the adrenal gland which liberates epinephrine and mobilizes glucose from glycogen. The regulation of blood sugar levels depends upon the activity of the liver which is influenced by the various aforementioned hormones.

NORMAL VALUES

The usual concentration of glucose under normal conditions varies from 90 mgm. to 120 mgm. per 100 ml. of whole blood. Blood sugar values depend a good deal upon the method employed in analysis. Analytical methods are based on the ability of glucose to reduce metallic compounds, chiefly those of copper (see aldehydes Chap. 12). Other reducing substances may be present in blood which tend to give higher than actual values. The glucose content of the erythrocyte is slightly less than that of plasma —approximately three-fourths of that of plasma. The plasma glucose level is subject to rapid changes while that of the cells tends to be more stable. Arterial blood contains approximately 5 mgm. more glucose per 100 ml. than venous blood except during starvation when both values approximate each other. Race and sex have no apparent effect on the fasting blood sugar values. Blood sugar is increased during exercise and decreased during exhaustion. Extremes of temperature and emotional disturbances have a tendency to increase blood sugar. Glucose is filtered by the glomerulus but is reabsorbed by the tubules so that none passes into the urine unless a threshold level is exceeded or a pathologic state is present.

EFFECTS OF ANESTHESIA

It is well established that glycogen may be mobilized during anesthesia and elevate blood sugar. Ether, chloroform anesthesia and anoxia produce notable increases. Morphine and other narcotics causes less pronounced elevations of blood glucose levels. Less significant changes occur during avertin and barbiturate narcosis. The level of hyperglycemia attained depends upon the amount of depression or depth of anesthesia. During cyclopropane, halothane, vinyl ether, ethylene, nitrous oxide, spinal epidural and local anesthesia little or no significant changes in the blood glucose occur if these are not complicated by anoxia. Muscle relaxants cause no changes. Anoxia superimposed upon anesthesia causes pronounced hyperglycemia. The source of the bulk of the glucose is presumably the glycogen of the liver since this is depleted during anesthesia. A number of factors are involved in the increases in blood levels. Release of epinephrine, depression of enzyme activity, asphyxia, blood loss and sympa-

thetic stimulation all contribute since they occur at one time or another during anesthesia and operation. The rise noted during ether anesthesia may be as high as 100% of the control level, sometimes even more. The rise is immediate, as a rule and reaches its maximum within 15 minutes. After the initial rise, there may be a progressive but less pronounced increase for the duration of the anesthesia. A return to normal occurs within 24 hours. The rise during cyclopropane anesthesia varies from 8% to 30% above the pre-anesthetic level. Inactivation of the adrenals in experimental animals, such as the cat, prevents or partially inhibits this hyperglycemia. Sympathectomy likewise inhibits the rise but does not completely abolish it. Diets rich in carbohydrates have been found to inhibit rises. The consensus is that the rise is the result of sympathetic stimulation. This may be explained in a number of ways: (1) Epinephrine is liberated which mobilizes the glucose from liver glycogen. (2) Norepinephrine is liberated by the influence of the anesthetic drug and acts as does epinephrine. (3) The autonomic centers in the midbrain are either inhibited or stimulated, producing sympathetic effects which cause the rise.

Blood sugar in rabbits under the influence of insulin is little affected by asphyxia or anoxia. Ether anesthesia given to rabbits under similar circumstances produces only a slight, if any, rise. Insulin administered after hyperglycemia is established causes the blood sugar to fall. More insulin is required in dogs in whom a hyperglycemia is established by ether to restore the blood glucose to its normal level than if insulin were administered before induction of anesthesia. Preliminary treatment with insulin and glucose causes glycogen to be deposited in the liver. Insulin given to a depancreatized dog anesthetized with ether has little effect on the hyperglycemia. Ether, therefore, neutralizes the action of insulin if the glycogen of the liver is depleted. Insulin also prevents the hyperglycemia of morphine.

GLYCOGEN

GLYCOGENESIS AND GLYCOGENOLYSIS

Glycogen, which is often called animal starch, resembles starch in many ways. It is the form in which carbohydrate is stored in animal tissues. *Glycogen is a* glucose polymer in which glucose molecules are united through glucosidic linkages between C_1 and C_4 or between C_1 and C_6. Approximately 9/10th of the ingested carbohydrate is stored as fat and 1/10th is stored as glycogen. Glycogen is found chiefly in liver and muscles. The usual content in the liver ranges from 0.2% to 10% by weight although the quantity varies with the nutritional and physiological state of the organism. The quantity in muscle also varies but is more constant, 0.2% to 1.8%. The hydrolysis of glycogen ultimately yields glucose both in vivo and in vitro. The breakdown of glycogen to glucose is known as *glycogenolysis.* The breakdown of glycogen to glucose is controlled by two specific enzymes. Three steps are involved. In the first phosphoglucomutase converts glycogen to glucose 1 phosphate. Then this is next converted to glucose 6 phosphate by glycogen phosphorylase which in turn converts it to glucose. The reverse process occurs utilizing the same enzymes. The build-up of glycogen from glucose is called *glycogenesis.* As has been mentioned, glycogenolysis is hastened by epinephrine, norepinephrine, or sympathetic nerve stimulation. Glycogen is deposited in muscles as well as liver through the influence of insulin. Adrenalectomy and adrenal insufficiency cause

a depletion of tissue carbohydrate reserves. The regulation of blood sugar content is a function of the balance between glycogenolysis and glycogen synthesis. Glucagon, the pancreatic hyperglycemic factor also causes hepatic glycogenolysis probably by activating the hepatic phosphorylases (Chap. 35).

GLYCOGENOLYSIS DURING ANESTHESIA

Glycogenolysis occurs during general anesthesia with various agents but mostly with *ether* and *chloroform*. Although normal livers vary widely in glycogen content and studies of the glycogenolysis are complicated by this fact, it is generally agreed that anesthesia does deplete these carbohydrate stores. No elevation in blood sugar occurs after hepatectomy. The depletion accompanying ether begins promptly after onset of anesthesia (approximately five minutes) and progresses gradually during the period of anesthesia. A concomitant rise in blood glucose levels occurs. This rise is most likely related to sympathetic stimulation, epinephrine release, or disturbances of enzyme activity. *Chloroform* causes depletion of glycogen and hyperglycemia similar to and in some cases more severe than ether. Muscle glycogen also decreases during *ether* anesthesia but not like that of liver. Certain *barbiturates*, amytal and dial, cause some decreases of liver glycogen and slight rises in blood sugar. *Anoxemia*, *morphine* anesthesia, and basal narcosis with *tribromethanol* also cause similar disturbances in carbohydrate metabolism.

UTILIZATION OF MUSCLE GLYCOGEN

The utilization of glycogen by muscle for energy of contraction has been extensively studied. Glycogen is first converted to hexoses which are quickly changed to lactic acid *anaerobically*, during which reaction the energy for contraction is liberated. In the presence of oxygen, 4/5ths of the resulting lactic acid is resynthesized to hexose and glycogen and 1/5th is oxidized to carbon dioxide and water to supply the energy of resynthesis and that used for muscle contraction. The anerobic reaction is rapid and allows the muscles to obtain energy very quickly. The aerobic reaction is slower and for the most part occurs in the recovery phase of muscle activity. The details of the utilization of carbohydrate by muscle are too involved for any discussion here. It might be said briefly, however, that glycogen is first converted to hexose phosphoric acid. The hexose phosphoric acid ester is probably fructose diphosphate which splits into two molecules of dihydroxyacetone phosphoric ester. These in turn form phosphoglycerol and phosphoglyceric acid. The latter is converted to phosphopyruvic acid which in turn is converted to pyruvic acid. The pyruvic acid combines with dihydroxyacetone to form lactic acid and phosphoglyceric acid. Two other substances besides carbohydrate are needed for the contraction—adenyl triphosphate and phosphocreatine. The adenyl triphosphate breaks down to phosphoric acid and adenylic acid. The phosphoric acid combines with hexose to form hexose phosphate. Phosphocreatine liberates phosphoric acid to combine with the adenylic acid which combines to form adenyl triphosphate. The utilization of glycogen by muscle during anesthesia appears to progress without sufficient restraint to inhibit activity of muscles carrying out ventilatory functions. In the presence of anoxia, lactic acid accumulates in blood and gives rise to metabolic acidosis. This is discussed in Chapter 29.

Cerebrospinal Fluid and Other Special Body Fluids

DISCONTINUOUS BODY FLUIDS

CERTAIN DISCONTINUOUS COLLECTIONS of body water of varying composition are referred to as the *transcellular* compartments. These include the cerebrospinal fluid, the intra-ocular fluid, the intraperitoneal pleural and pericardial fluid, the fluid in the gastro-intestinal tract and the synovial fluid. Although each of these is of importance in its own right the cerebrospinal fluid is the one of significant importance to anesthetists.

CEREBROSPINAL FLUID FORMATION

Cerebrospinal fluid closely resembles a diluted protein-free blood filtrate in both composition and appearance. The fluid is elaborated from the blood by the choroid plexus. Controversy has existed as to whether or not spinal fluid is a filtrate or is secreted by the choroid plexus. However, thermodynamic data indicate that the fluid is not a simple filtrate because more energy is involved in its formation than would be accounted for by filtration. The fluid eventually returns into blood via the venous sinuses and through the cerebrospinal veins by filtration through the arachnoid villi. The villi dip into the fluid from all surfaces of the arachnoid, both cephalic and spinal. True solutions readily pass through the arachnoid villi; colloids pass more slowly. The rate of diffusion depends upon the size of the molecule. The greater portion of the fluid is absorbed from the villi in the skull since they are more numerous here. Diffusible dyes introduced into the subarachnoid space readily pass into the venous blood and can be detected there. Slow passage of spinal fluid into the lymph channels along the perineural spaces has also been demonstrated. Reabsorption depends upon the difference between the colloid osmotic pressure of the blood and the osmotic pressure of the fluid. The latter represents the difference between subarachnoid fluid pressure and the intracranial venous pressure. The hydrostatic pressure fluctuates with positional variations. The rate of absorption, therefore, varies with activity and other conditions over a 24 hour period.

LYMPHATIC FUNCTION

Cerebrospinal fluid is believed to function as lymph. All tissues except those of the central nervous system have lymphatics. Therefore, it is understandable why this suggestion has been made. The purpose of lymph is to return proteins and other macromolecules in transudates arising from capillaries and cells to the vascular system.

SPINAL FLUID AND BLOOD-BRAIN BARRIERS

Certain substances readily pass from blood to brain or from blood to cerebrospinal fluid or from fluid back to blood; others encounter a barrier. Distinctions are made between (1) the cerebrospinal fluid brain barriers, (2) the blood cerebrospinal fluid barriers and (3) the blood-brain barriers. Of the three the blood brain and the blood cerebrospinal fluid have been studied in greater detail. The presence of the blood-brain barrier was first suggested by Erlich who noted that analine dyes injected intravenously stained all tissues except those of the central nervous system. Subsequent studies by numerous other workers using dyes, colloidal solutions or isotopes of various elements have led to the generalization that the barrier is a homeostatic mechanism designed to consistently maintain an optimal environment for the neurons of the central nervous system. Studies using ions of radioactive sodium, potassium, bromine, rubidium, strontium and so on indicate that there is a lag in passage of substances from the blood into the cerebrospinal fluid. This lag is designed to prevent abrupt changes in solute concentration. The delay is selective—that is, some ions, as for example sodium, pass through sooner than others, such as potassium or calcium. Considerable importance has been attached to the blood brain barrier as a factor in rate of uptake of anesthetics by nervous tissues (Chap. 3). Some workers question the existence of a blood-brain barrier as a barrier and have proposed that lipoid solubility is the important factor in the variations in accessibility of foreign substances to the brain. There is evidence available to support this hypothesis. The outward diffusion of substances from spinal fluid into the blood apparently occurs more rapidly than the inward. More will be said of this later.

The transfer of substances from the spinal fluid to the intercellular spaces of nervous tissues occurs rapidly. The intercellular fluid of the nervous system together with the cerebrospinal fluid might be considered as an extracellular fluid double compartment system in which the solutes in each have ready and rapid access into either space. The rapid transfer from the cerebrospinal fluid to cells is in sharp contrast to the slow, gradual change which occurs from blood to cerebrospinal fluid compartment.

VOLUME

The total volume of cerebrospinal fluid in the adult averages 130 ml. The volume of fluid in the spinal canal approximates 20 ml. The rate of formation of cerebrospinal fluid has not been definitely established and is probably quite variable. Some data, not confirmed, indicate that complete change and replacement with newly formed fluid occurs every three hours. Compensatory mechanisms to offset loss by leakage are present. This will be discussed later.

CEREBROSPINAL FLUID PRESSURE

The cerebrospinal fluid is under pressure. Cerebrospinal fluid pressure is subject to variations. The term intracranial pressure is often used interchangeably with cerebrospinal fluid pressure. In the recumbent position, the cerebrospinal fluid pressure averages 110 to 130 mm. of water. In the horizontal position pressures are the same in the lumbar region as they are in the occipital regions. In the sitting position, on the other hand, the pressure in the lumbar region is ap-

proximately 200 mm. higher than in the cisterna.

Variations in cerebrospinal fluid pressure occur with changes in (1) the volume of the fluid in the system, (2) the brain volume, (3) the venous blood volume, (4) the rate of intracranial blood flow, (5) the elasticity of the membranes covering the brain and (6) abrupt changes in composition of the blood. Any increase in one or more of these factors increases the intracranial pressure. Intravenous injection of hypotonic solutions causes an increase in pressure while hypertonic solutions of salt, glucose and urea and other substances decrease the pressure. Presumably water passes through the membrane more easily and more rapidly than the ions or molecules of solute which also pass but lag behind the water. When hypertonic solutions are administered the water migrates outward into the plasma. Later the substance passes into the spinal fluid and water returns inward restoring the pressure to previous levels and giving rise to the phenomenon known as "rebound." When hypotonic solutions are infused into blood the water migrates inward into the subarachnoid space. This is the rationale behind the use of hypotonic solutions in the fluid depletion syndrome such as follows lumbar puncture (spinal headache).

The extracellular compartment of the central nervous system is similar in chemical composition to the extracellular fluid of other tissues in other areas of the body. However, it behaves differently than spinal fluid when water is added or removed from the body. This compartment is incapable of rapid solute transfer, therefore, isotonicity is accomplished by the transference of water.

EFFECTS OF FLUID DEPLETION

There are homeostatic mechanisms which tend to maintain the cerebrospinal pressure near normal when fluid is repeatedly removed in small amounts over long periods of time or when it leaks from a perforation in the dura. Three possibilities are involved in maintaining this homeostasis: (1) increased fluid formation, (2) collapse of the dura and (3) increase in volume of the venous blood in the cerebrospinal circulation. Should the volume of fluid be artificially increased by infusion, for example, a mechanism for its removal and maintaining homeostasis is also present. However, this compensatory mechanism does not operate as efficiently as the one for making up for the loss of fluid. The greater the quantity of cerebrospinal fluid removed at a single sitting the greater the decrease of the spinal fluid pressure. This loss can be compensated for by the infusion of isotonic saline. The quantity of isotonic normal saline required to re-establish the initial cerebrospinal fluid pressure does not equal the quantity removed. In other words, some fluid forms in the meantime. Vasodilatation is believed to augment the formation of fluid when the volume is depleted. The use of intravenous alcohol, nicotinic acid and other vasodilating drugs is based upon the assumption that the vasodilatation they cause in the choroid plexus augments the formation of cerebrospinal fluid.

Increases or decreases in volume and in pressure result in headache. The so-called "spinal headache" is believed to be caused by slow leakage of fluid from the subarachnoid space which in turn causes reduction in volume and pressure. Restoration is attempted by use of some

of the aforementioned measures—i.e., hypotonic solutions intravenously or by the use of vasodilators. Some success has been reported with direct replacement of fluid with isotonic saline. Attempt to retain body water by promoting antidiuresis with pitressin or corticosteroids has also been suggested. *Compression of the dura by injecting isotonic saline into the peridural space has also been suggested and has met with varying degrees of success.*

CIRCULATION OF FLUID

There is no actual circulation of spinal fluid in the subarachnoid space. The fact that the composition in the lumbar area differs slightly from that in the cephalic region is evidence of this. Pulsatile excursions of fluid may be observed in the column of fluid in a manometer attached to a needle in the lumbar area with each heart beat and with respiratory movements. Variations in venous and arterial blood pressure produced by coughing, straining and similar activity may cause secondary changes in cerebrospinal fluid pressure and set up eddy currents in the fluid in the spinal canal. This may influence the (cephalad) ascent of spinal anesthetic drugs.

COMPOSITION

APPEARANCE AND DENSITY

Cerebrospinal fluid is a clear, colorless, liquid whose specific gravity varies from 1.003 to 1.009 but usually averages 1.006 at 37°C. Specific gravity values vary from individual to individual because of individual variations in composition. Discrepancies in "normal" values are numerous. Usually the figures are too low. These discrepancies arise from the fact that determinations were made at room temperature instead of body temperature. Precise determinations must be made by collecting the fluid under oil to prevent loss of carbon dioxide and water, both of which account for some loss in density. The determination is made at 37°C. *Specific gravity is of a particular interest in spinal anesthesia where consideration is given to gravitational and diffusional effects upon solutions of local anesthetics. This is discussed further on in this chapter.*

Cerebrospinal fluid contains mostly electrolytes and diffusible organic constituents of plasma and slight traces of protein.

PROTEIN CONTENT

The protein content of cerebrospinal fluid is low, less than 40 mgm. per 100 ml. of fluid. Most of this protein is albumin. The albumin-globin ratio is 3:1. There is no fibrinogen present, normally. *The protein content is slightly greater in the lumbar than in the cephalic pool* presumably due to the gravitational effects induced by the upright position. In general, the electrophoretic pattern is the same as that of serum protein. There is, however, a rapidly migrating protein component *detectable in the electrophoretic pattern. This fraction is believed to originate from the nervous tissues and not from the plasma.*

Proteins are increased in certain pathological conditions, in the presence of tumors, infections and hemorrhagic diseases. The protein in these situations may be of a type not normally found in the spinal canal. These may be identified by different precipitation reactions and other specific tests, such as the colloid gold test.

ELECTROLYTE CONTENT

HYDROGEN ION CONCENTRATION

Spinal fluid is distinctly *alkaline* and possesses the same pH as blood; namely, 7.35 to 7.40. Quoted values in texts do not agree because data in many cases were obtained at room temperature instead of body temperature and the fluid was not collected anaerobically. The chief buffer pair in cerebrospinal fluid is the bicarbonate-carbonic acid pair. The pH determinations done on specimens exposed to air are more alkaline than those collected anaerobically because carbon dioxide is lost to the air. The basicity is due primarily to the presence of the bicarbonate ion. The bicarbonate ion concentration approximates that of blood. Approximately 40 to 60 volumes per cent carbon dioxide may be liberated from cerebrospinal fluid. Inorganic phosphates are approximately half the blood concentrations (2 mgm. to 5 mgm. per 100 ml. for blood and 1.25 mgm. to 2 mgm. per 100 ml. for cerebrospinal fluid). They account for only a small part of the buffering action.

CATIONS

The concentration of sodium ion is the same for both plasma and spinal fluid. It averages 141–2 m.Eq. per liter. Potassium is found in the same concentration as blood 3.3 m.Eq. per liter. Magnesium, for some peculiar reason, is found in somewhat higher concentration in cerebrospinal fluid than in blood (1.2 m.Eq., blood 0 80 m.Eq. per liter). Calcium values are approximately half those found in blood (1.25 m.Eq , blood 2 5 m.Eq. per liter). The calcium probably represents the diffusible portion of calcium of plasma. The protein bound portion does not pass into the spinal fluid.

ANIONS

Chloride ion is found in higher concentrations than in plasma. Normally it averages 124 m.Eq. per liter compared to 101 m.Eq. in blood. This is due to the Donnan effect. Iodine exists only in one-fourth the normal concentration of plasma.

ORGANIC SUBSTANCES

Cholesterol and lactic acid are ordinarily not normal constituents of cerebrospinal fluid but may be found in pathological states. Urea is a highly diffusible substance and, therefore, passes readily into spinal fluid. Concentrations in cerebrospinal fluid are the same as in plasma and other body fluids. Uric acid and creatinine are found in approximately half the concentration of blood. Amino acid levels are one-fourth to one-fifth those of blood. Glucose levels are approximately half those of blood. The concentration in the ventricles is slightly greater than in the lumbar area. The presence of blood in spinal fluid lowers the glucose concentration due to the effect of glycolytic enzymes which are added by the extravasation. The glucose *level is reduced when inflammatory lesions* of the nervous system are caused by bacteria capable of metabolizing sugars.

Enzymes originating in the nervous system, particularly true acetyl choline esterase, are found in the cerebrospinal fluid. Those normally found in blood are not present. Proteins believed to arise from the nervous tissues have been found also. Both the proteins and the enzymes are increased in brain injuries and convulsive disorders.

PASSAGE OF DRUGS FROM BLOOD TO CEREBROSPINAL FLUID

Many drugs pass from the general

circulation into the cerebrospinal fluid. The problems of drug penetration at the blood-central nervous system barriers are quite complex. Details concerning the rate of penetration, the concentration and time for attainment of equilibrium are meagre even for the commonly used drugs. The lipophilic nature of anesthetics and many hypnotics cause them to be concentrated, at one time or another, in the brain in greater quantities than in other tissues. One would suppose that these substances would abound in the cerebrospinal fluid. This does not seem to be the case, however. Factors other than barrier permeability are involved. The concentration of ethyl alcohol parallels that of blood. It is worth mentioning that alcohol is not strongly lipophilic. The concentration of tribromethanol is approximately half that of blood. Barbiturates are found in concentrations equal to those of plasma. Levels in no way reflect the concentration present in the brain. The thiobarbiturates of the ultra short acting type (thiamylal, thiopental) easily pass the blood-brain barriers and are present in greater concentration there. The ordinary (oxy) barbiturates do not penetrate the barriers as easily and are, therefore, more uniformly distributed in the watery tissues and body fluids. The thought was once quite prevalent that barbiturates were concentrated in cerebrospinal fluid in cases of overdosage. In fact, withdrawal of the fluid was recommended to deplete the brain barbiturate level and to relieve symptoms. Kozelka and Tatum, however, determined the barbiturate concentration in cerebrospinal fluid pooled from a group of patients who had ingested large amounts of barbiturate for suicidal intent. Barely detectable levels were found.

Most of the available data on concentration of central nervous system depressants in cerebrospinal fluid is concerned with non-volatile drugs. Data on the concentration of volatile agents are meagre. The fact that they all easily diffuse through membranes strongly favors the belief that the spinal fluid level equals plasma level.

BEHAVIOR OF NON-ANESTHETIC SUBSTANCES INJECTED INTRATHECALLY

It has been generally accepted that drugs pass more readily from the spinal fluid into the blood than vice versa. However, the behavior of vasopressors injected intraspinally along with the anesthetic agents suggests that this may not necessarily be the case. No significant elevations in blood pressure follow the intrathecal injection of vasopressors combined with the spinal anesthetic agent. This appears to be the case with both the catechol amine type compounds which are rapidly metabolized in the blood, and the stable compounds which are not. Cardiac irregularities do not occur when vasopressors are administered intrathecally in conjunction with the spinal anesthetic agent and cyclopropane is subsequently administered. Serious arrhythmias appear when the drug is deposited in the interspinous ligaments. These findings further support the idea that these drugs pass slowly from the subarachnoid space. Ventricular fibrillation occurs in dogs when spinal fluid withdrawn at intervals of 1 to 3 hours after intraspinal injection of epinephrine is injected intravenously. This suggests that destruction of epinephrine in the spinal canal occurs slowly if at all and that absorption into the blood stream is a slow process also. Epinephrine is destroyed once it passes into the blood. Weiland, Brok-Kahn and Minsky have

reported that levels of dextrose remain elevated for more than one hour after the intrathecal injection of dextrose. No hyperglycemia could be demonstrated.

SPINAL ANESTHESIA AND CEREBROSPINAL FLUID

The constituents of spinal fluid which could possibly react with or interfere with the action of local anesthetic substances are of special interest to the anesthesiologist. Spinal fluid is alkaline; the possibility must be entertained that local anesthetic drugs, since they are salts of poorly soluble, weak bases, may precipitate from solutions when injected intrathecally. The alkalinity of spinal fluid is due, as has been mentioned before, to the bicarbonates of sodium and potassium. The carbonic acid-sodium bicarbonate pair is the important and most abundant buffer pair in the cerebrospinal fluid. Phosphates and protein concentrations are too low for these to be of importance as buffers. The acid entering into the salt formation of the local anesthetic reacts with the bicarbonate. Sodium chloride, the free base of the drug and carbon dioxide are the *end products. The quantities involved* are not sufficient to cause precipitation, however. Knight and his co-workers have reported that the various local anesthetics in the form of their hydrochloride salts added to spinal fluid in the usual anesthetic doses did not decrease the pH to less than 7.2 and that no precipitation resulted from the combination. Procaine hydrochloride (pH 5.35) resulted in a final pH of 7.20. The pH after the addition of enough sodium hydroxide to liberate the free base in sufficient quantities to produce a cloudiness was 9.4 Dibucaine hydrochloride (Nupercaine) pH 6.02 gave a pH of 7.4 with spinal fluid and precipitated at a pH of

8.35 after the addition of sodium hydroxide. Tetracaine hydrochloride (Pontocaine) at pH 3.30 gave a pH of 7.22 and precipitated at 8.10; piperocaine hydrochloride (Metycaine) pH 4.00 gave a pH of 7.15 and precipitated at pH 8.05. Thus, the intrathecal precipitation of the local anesthetics commonly used for spinal anesthesia is unlikely. Precipitation and cloudiness seen after mixing the drug with spinal fluid and allowing the mixture to stand in air is probably due to hydrolysis of the ester and precipitation of one or both of the products of hydrolysis. There is no reason to believe that substances other than sodium bicarbonate in spinal fluid interact with the currently-used anesthetic drugs.

SPECIFIC GRAVITY

The relationship of specific gravity of the anesthetic solution to that of spinal fluid is important, if control of the level of anesthesia is to be precise. Solutions of local anesthetic drugs which have a specific gravity equal to that of spinal fluid are termed *isobaric;* those whose specific gravity is greater are termed *hyperbaric;* while those which are lighter *than spinal fluid are called hypobaric.*

HYPERBARIC SOLUTIONS

Generally, solutions which are obviously hyperbaric or hypobaric are used in order to control the level and the intensity of anesthesia. Hyperbaric solutions gravitate caudad if the body is inclined in the head-up, supine position after injection while hypobaric solutions migrate cephalad. Solutions are usually made hyperbaric by weighting with plasma, dextrose (10%), inositol or by using small volumes of concentrated solutions of the less potent agents, such as procaine. The dextrose is slightly on the acid side of neutrality. However, the

total quantity of acid in glucose is so little that it has little influence on the overall hydrogen ion concentration of the total volume of solution or spinal fluid in the lumbar area. Inositol has been used with certain local anesthetics not compatible with dextrose (Ravocaine). The dextrose solution is not only heavier but more viscous than water. Thus, it permits control of the level because it glides through the spinal fluid when the patient is tilted. The glucose mixes rapidly with the spinal fluid in the dural sac—within one to two minutes. After this time one can anticipate little movement of the mass which can be ascribed to the viscous, heavy nature of the solution. The less potent drugs, such as procaine, hexylcaine, or piperocaine, which are used in comparatively greater quantities (120 mgm. to 150 mgm.) than the more potent ones like tetracaine or dibucaine may be made up in small volumes of concentrated solutions dissolved in spinal fluid or saline. These may then be used to give weight to a solution of a potent drug such as tetracaine. Even when used alone solutions of procaine of more than 5% strength are hyperbaric. The potent drugs, such as tetracaine and dibucaine which are used in relatively smaller amounts (20 mgm.) are dissolved in the concentrated procaine. The quantity of drug used is small and the resulting solution, even with minimal volumes, is definitely hyperbaric. Such solutions rapidly intermix with the spinal fluid. The sliding effect does not last as long and, therefore, control of the level of anesthesia is not as precise as it is with glucose mixtures.

Isobaric Solutions

Isobaric solutions are no longer employed due to their lack of controllability. When this technique is used it is generally assumed that cerebrospinal fluid has a specific gravity of 1.006. The results obtained with isobaric techniques are unpredictable and variable. Anesthesia is often spotty. The direction in which the drug migrates is unpredictable since the specific gravity of spinal fluid varies from one patient to the next. The specific gravity of cerebrospinal fluid, should one care to employ this technique, may be determined at the time of lumbar puncture by adding a drop or two to a mixture of brombenzine and xylol of known specific gravity. The mixture is prepared in such proportions that the specific gravity corresponds to that of the solution of the drug one contemplates using. One can thereby determine whether or not the solution being employed is hyperbaric or hypobaric for a given patient. The simpler, and perhaps the safer, expedient is to add substances which either increase or decrease the specific gravity of the solution of the drug so that it is well above or well below the usual normal specific gravity of cerebrospinal fluid. Any solution prepared by adding crystals to *spinal fluid* (not distilled water) is hyperbaric. It may not be sufficiently hyperbaric to be technically suitable, however.

Hypobaric Solutions

Hypobaric solutions are prepared by dissolving the drug in distilled water, hypotonic saline solution or by adding absolute alcohol not to exceed 10% of the final volume. The addition of alcohol is looked upon with disfavor due to the possibility of initiating neuropathies. Hypobaric solutions are practical only when potent local anesthetics, such as dibucaine are used. Doses less than 5 mgm. per ml. are usually employed. These are distinctly hypobaric. Dibucaine is occa-

sionally used in a mixture referred to as Jones's solution. One part of the drug is dissolved in 1500 parts of 0.5% aqueous sodium chloride. The specific gravity at 20°C. is 1.0025. Two per cent aqueous solutions of procaine are closely isobaric (S.G. 1.005). A 1% solution of tetracaine in 0.67% saline is closely isobaric, having a specific gravity of 1.0067 at 25°C.

EFFECTS OF TEMPERATURE

The onset of anesthesia is influenced by the temperature of the solutions injected. The latent period is shortened by warming the solution to body temperature. Volumes of local anesthetic solutions of 3 or 4 ml. injected intrathecally quickly attain body temperature. Large volumes, as in the case of Jones's solution in which case 10 or 15 ml. are used, must be warmed to body temperature, otherwise the onset of anesthesia is delayed.

MISCELLANEOUS FACTORS INFLUENCING SPINAL ANESTHESIA

The direction in which the bevel of the needle is directed at the time of injection plays little or no part in determining the level to which spinal anesthesia extends. Much nonsense has been written about this unimportant, picayune detail. The solution is forced directly forward regardless of the direction in which the bevel faces. The spinal fluid pressure likewise bears no relation to the dermatome segment to which the block extends. The molecular diffusion of local anesthetics is likewise insignificant in establishing levels. One should however distinguish between turbulence and true diffusion. True or molecular diffusion consists of intermingling of the molecules of the drug with those of the solvent and the spinal fluid. True diffu-

sion in liquids is a slow process which may require hours or days before the mixtures become homogenous. Molecular diffusion bears no relationship to turbulence or gravitational effects. Most of the migration of local anesthetics intraspinally is due to turbulence which is initiated by the force of the injection, to volume displacement, or to the gravitational effect of liquids of different specific gravity aided by position. Circulation of spinal fluid and the pulsations due to the heart beat or respiration, likewise, have no effect on the level of spinal anesthesia which is attained. Increases in venous pressure in the abdominal veins is transmitted to the prevertebral and intraspinal venous plexus. This in turn causes a decrease in subarachnoid volume in the vertebral column. This in turn is followed by cephalad displacement of the spinal fluid and whatever local anesthetic is present. "High" spinal anesthesia which inadvertently results from straining or any other maneuver which elevates the venous pressure in the abdominal veins is believed to result from this change in hemodynamics.

DISAPPEARANCE OF DRUGS FROM THE SUBARACHNOID SPACE

The manner and rate of disappearance of local anesthetic drugs from the spinal fluid after intrathecal injection are of interest to the anesthesiologist. It has been stated, rather empirically, that the outward transfer of substances from the cerebrospinal fluid to the blood is more rapid than the inward transfer. Recent studies with radioactive isotopes confirm this belief. However, this free outward passage does not hold for some substances. Blood and its breakdown products may persist in spinal fluid for days. Radiopaque materials likewise are

known to remain in the subarachnoid space for many days. The diffusible substances obviously leave the space at a much more rapid rate. Yet, there are certain substances which persist for a longer time than would ordinarily be anticipated even though they are diffusible.

Studies on the rate of elimination of local anesthetics are not too numerous. Some of the data is conflicting. A number of variable factors are no doubt responsible for the conflicting data. The volume of fluid injected, the dilution factor, volume of spinal fluid, the chemical nature of the drug, the rate of penetration into or uptake by nerve tissue, and the rate of absorption into the blood are all variable factors which are difficult to assess and to control. The bulk of the evidence indicates that the concentration of the local anesthetic at the injection site falls quickly—within minutes. Koster and his coworkers studied the disappearance of procaine during spinal anesthesia in man. They injected 150 mgm. of the drug dissolved in 3.5 ml. of spinal fluid in the second lumbar space. The initial concentration at the injection site averaged 43 mgm. immediately after injection. Within five minutes this fell to 2.9 mgm. per ml. of cerebrospinal fluid. The decline in concentration from then on occurred at a slower rate, requiring over an hour for almost complete disappearance. The curve initially is parabolic then a straight, declining plateau. Labat also reported similar findings. Bullock and MacDonald also noted that concentrations of local anesthetic drugs injected into the subarachnoid space of cats fell rapidly at the site of injection. The concentration is greatest, as one would suspect, at the site of injection and falls as one ascends the cord. The quantity of drug absorbed into the systemic circulation and excreted into the urine is negligible. Bul-

lock found, in each case, that it amounted to less than 3% of the injected dose. The concentration in the blood during anesthesia was likewise examined. In man, a half hour after induction the concentration of procaine was less than 0.002%. Apparently the systemic absorption is extremely slow and accumulation is negligible. These are data of older workers. Workers in recent years have reported essentially similar findings.

INFLUENCE OF VASOPRESSORS ON ABSORPTION

In recent years vasopressors have been added to solutions of the local anesthetics to intensify and prolong the action. Of these epinephrine and norepinephrine are the most effective. The duration of action is prolonged as much as 60% with epinephrine and 55% with norepinephrine. Absorption of the local anesthetic drug is retarded by vasoconstriction. The vasoconstrictors themselves are also slowly absorbed. Systemic pressor effects are seldom observed following the intrathecal use of epinephrine, norepinephrine, ephedrine or other sympathomimetic drugs. One hour after injection of procaine and epinephrine intraspinally the author and his associates were able to produce ventricular fibrillation in dogs anesthetized with cyclopropane when the spinal fluid was withdrawn and injected intravenously. This indicated that the amine was still present and had undergone no change. No pressor responses were noted nor were there any cardiac irregularities even though the animals were anesthetized with cyclopropane.

Converse and his associates have measured the decline in concentration of tetracaine combined with dextrose and epinephrine and compared the variations in concentration with controls in which

no epinephrine was used. The concentration of tetracaine in samples withdrawn 5 and 10 minutes after injection were higher in those to which epinephrine had been added than in those without it. After 30 minutes more tetracaine was present in those in which epinephrine was used. The pattern of the curves for the decline in concentration was similar to those obtained by previous workers. Vasopressors do not alter the physical properties of the anesthetic drug nor do they potentiate their effects directly. The evidence that they act by retarding absorption is not conclusive but is more than suggestive.

CRITICAL LEVELS OF DRUGS

Exact information on the minimal concentration of local anesthetic agents in the cerebrospinal fluid necessary to block different types of nerve fibres is not available. Much data has been published but much of it is conflicting and of little practical significance. Many of the figures available are not accurate because the function of the individual nerve fibre studied is not specified. The concentration obviously varies with the nature of the drug, the type of fibre and the size of fibre. It is generally stated that about half the concentration is necessary to block sensory fibres as the motor fibres. The validity of this statement is open to question. Brodie, Helrich and their co-workers found by introducing catheters intrathecally that the critical level for procaine in man was 0.2 mgm. per milliliter for the disappearance of sensory anesthesia. Figures for other drugs are not available.

EFFECT OF CHEMICAL AGENTS ON NERVE TISSUE

The most feared of the neurologic com-plications following spinal anesthesia is paraplegia due to arachnoiditis, myelitis and other non-specific inflammatory processes involving the cord and its coverings. This symptom-complex is often referred to as the "cauda equina syndrome." Fortunately this complication is extremely rare, but when it occurs it is catastrophic. Thus, it is understandable that clinicians have focused their attention on the role that the chemicals employed for inducing the block may have in causing degenerative and irritative lesions.

Most of the available evidence discounts local toxicity of the anesthetic drug as the major factor in causing neurologic complications. Too many spinal anesthetics using a variety of drugs have been administered too many times to too many patients without any complications whatever to give any credence whatever that these drugs are neurotoxic. Some other factor besides contact with the chemical is involved. Contaminants, either bacterial or chemical, have been incriminated. Among the chemical substances which might possibly play a role are detergents used for cleansing, antiseptics for cleansing the skin or caustic agents used for cold sterilization of glass ampules. The possibility that improperly prepared solutions are responsible cannot be discounted. The possibility that the drug may precipitate in the spinal canal due to alkalinity and cause damage to the cord has been suggested but has no factual basis. This is discussed in previous paragraphs.

TONICITY OF SOLUTIONS USED FOR SPINAL ANESTHESIA

The possibility that tonicity of the solution used for spinal anesthesia may be a factor is unlikely and likewise may

be dismissed along with factors mentioned in previous paragraphs. Most solutions of local anesthetics used for spinal anesthesia are not isotonic. However the injected solution quickly disperses and mixes with the spinal fluid and becomes isotonic with the nervous tissue. The fact that hypotonic solutions injected intraspinally cause a temporary and prompt rise in venous pressure suggests that compensatory mechanisms for maintaining tonicity begin to operate promptly and correct the discrepancy quickly.

CHANGES IN COMPOSITION CAUSED BY SPINAL ANESTHESIA

Data on changes in composition of cerebrospinal fluid after spinal anesthesia are not in full agreement as far as details are concerned but agree in matters of generalization. Changes for the most part are transient and insignificant. The results vary with the technique, the drug, duration of the block and the time of examination of the fluid. In some cases the changes persisted for 24 hours or less; in others they persisted for three or four days. In most instances the changes are minor. In most cases the cerebrospinal fluid of patients undergoing operation using spinal anesthesia induced with procaine, tetracaine and piperocaine have been examined. The usual anesthetic doses of the drug were employed. Most workers report some increase in the number of cells. Usually these have been in the lymphocytes and not in the polymorphonuclear cells. The number varies but the increase is not significant and compares in no way with the leukocytosis due to bacterial infection. Several reports mention isolated cases in which the number of leukocytes has exceeded several thousand per ml.

The protein content, particularly the globulin, is increased in one-third of the patients receiving spinal anesthesia. Some increase in dextrose levels, and average of 3–4%, has also been observed. The colloidal gold curves are not altered, as a rule. No significant changes in the N.P.N., chloride and globulin levels have been observed for as long as three weeks after the lumbar puncture was performed. Changes which occur in the cerebrospinal fluid following spinal anesthesia apparently appear in the immediate post-anesthetic period and are transient and are not associated with any clinical signs or symptoms. One fact that is often overlooked is that in all the reported studies the effect of simple lumbar puncture itself without the injection of fluid or drugs may also cause changes. The tendency in the reports is usually to tacitly incriminate the drug.

INTRACRANIAL PRESSURE AND ANESTHESIA

The fact that all inhalational anesthetics increase intracranial pressure has been widely accepted. This is now known to be fallacious. Elevations in intracranial pressures during general anesthesia are insignificant if ventilation is adequate. Increases during anesthesia are due to vasodilatation. The most offensive agent in this regard is carbon dioxide. Thus, any factor which favors obstruction of respiration or hypoventilation tends to cause a retention of carbon dioxide which elevates the intracranial pressure. The vasodilatation in turn increases the brain volume and thereby the overall intracranial pressure. Morphine and narcotics of similar potency raise the pressure by decreasing ventilation. If the airway is patent and ventilation is augmented most inhala-

tional anesthetic agents cause slight or no increases in intracranial pressure. Chloroform, ether, vinyl ether, nitrous oxide, Fluothane, ethyl chloride, trichlorethylene and ethylene all cause no significant changes.

Anoxia causes a marked increase in intracranial pressure. There are two reasons for this. Anoxia is usually accompanied by carbon dioxide retention. Anoxia also causes an increase in permeability of the blood-fluid barrier. Anoxia of more than several minutes duration may raise intracranial pressure by increasing capillary permeability and causing a perivascular and pericellular transudation of fluid (cerebral edema).

Intracranial pressure influences systemic blood pressure. In an attempt to maintain a balance the blood pressure tends to parallel the intracranial pressure—an elevation causes a rise in blood pressure—a decline causes a fall. On the other hand the vascular system of the brain has autonomous control. An elevation in blood pressure does not necessarily cause a parallel proportionate increase in intracranial pressure. The brain protects itself from excesses in systemic pressure. Likewise in hypotensive states an attempt is made to maintain adequate cerebral blood flow. However, these mechanisms operate up to a point after which the intracranial pressure changes.

EFFECT OF DRUGS

Drugs which depress the vasomotor center and cause hypotension produce a concomitant fall in intracranial pressure. Certain basal narcotics allegedly cause a decrease in intracranial pressure. They do so by depressing the vasomotor center and causing the systemic blood pressure to fall which in turn causes the intracranial pressure to decline. Avertin,

hexobarbital and other ultra short acting barbiturates ordinarily cause no change but if circulatory depression is present they act in this manner. These drugs often cause an elevation in intracranial pressure because they depress the respiratory centers and produce hypoventilation. Pure oxygen causes some cerebral vasoconstriction and lowering of intracranial pressure. The brain volume is decreased during intentional hypothermia or hypotension with ganglionic blocking agents.

The intracranial pressure is elevated by coughing, straining, or bucking during intubation when a patient is light, by retching, vomiting, and struggling due to stormy induction and by airway obstruction, or agitation and excitement during recovery. Such elevations in pressure are associated with increases in venous pressure which in turn affects brain volume. The volume in the cranial vault is diminished during deliberately induced hypothermia. The fall in pressure is proportionate to the fall in venous pressure and averages 5.5% per degree Centigrade temperature reduction in the 35°–25° range.

CEREBRAL EDEMA

Cerebral edema (brain swelling) must be distinguished from inflation. The latter results from dilatation of the ventricles, blood vessels and cisternal. Inflation is caused by the same factors which cause increases in intracranial pressure. Inflation occurs quickly—in a matter of minutes. Swelling or edema on the other hand may be insidious in onset, comes about in a matter of hours or days and persists for some time. Inflation, with proper measures can be made to subside quickly; cerebral edema cannot. The mechanisms causing cerebral edema are not known with certainty.

Anesthesia and Liver Function

FUNCTIONS OF THE LIVER

THE ROLE OF THE LIVER in surgery is repeatedly stressed. The possible deleterious effects of anesthetics upon the liver have been recognized for some time. Changes in the functional status of the liver are difficult to evaluate since the functions are multiple and no technique of assessment evaluates them all simultaneously. The majority of tests give information on one function only. A detailed discussion of the functions of the liver is beyond the scope of this book. However, a brief resume is included to assure a clearer understanding of the data during anesthesia. Practically all hepatic functions are of a biochemical nature. Certain of these may be grouped together because they are closely related.

FUNCTIONS RELATED TO NUTRITION

(1) The first group of related functions includes those concerned with *nutrition*. The liver's role in nutrition and the metabolism of proteins, fats and carbohydrates is a matter of common knowledge. Not only are carbohydrates stored as glycogen, but various hexoses absorbed during digestion are converted to forms which can be used or stored by the organism. Fructose, galactose, mannose, and other sugars not utilizable by the body as such are transported to the liver and converted to glucose and glycogen.

Amino acids obtained by the hydrolysis of proteins pass from the gastrointestinal tract into the portal system and thence to the liver, where they are either utilized or distributed to the tissues. The unused amino acids are deaminized and converted to carbohydrates or fats. The nitrogen from the deaminization is combined with carbonic acid and is converted to urea which is eliminated as a waste product. Plasma proteins also are synthesized and stored in the liver. Fibrinogen, the protein so essential for blood clotting, prothrombin and heparin are also formed in the liver. Purines derived from nucleoprotein are converted to xanthines and then to uric acid which is excreted or destroyed.

The liver acts as a temporary storage for fats. Esterification of sterols with fatty acids, phosphorylization of fats and formation of unsaturated fatty acids also occur in the liver. Beta oxidation and formation of ketone bodies likewise occurs in the liver. It is worth noting that functions concerned with nutrition depend upon the capacity of the liver to alter substances chemically.

EXCRETORY FUNCTIONS

(2) The second group of similarly-related functions includes those concerned with *excretion* and *secretion* of various substances by the hepatic cells. The production of bile by the reticuloendothelial

system of the liver, bone marrow, and other tissues, and its subsequent excretion by the hepatic cells is a most important function. Bilirubin and biliveridin which are formed by degradation of hemoglobin are the two most important bile pigments handled by the liver. The liver also excretes drugs and other chemicals foreign to the body. The liver secretes bile salts, lipoids and other substances. These are then conveyed through the biliary passages to the intestinal tract or gall bladder.

(3) A third group of similar functions includes those concerned with the capacity of the liver to *store essential substances*. Besides lipoids, carbohydrates, proteins, the liver stores vitamins, enzymes and essential metals, such as iron, manganese, and copper and other vital substances in the hepatic cells.

DETOXIFYING FUNCTIONS

(4) A fourth group of similarly-related functions includes those dealing with the power of the liver to *detoxify or alter substances* foreign to the body. Detoxification, also known as biotransformation, is the biochemical conversion of a physiologically active substance to one which is physiologically inactive. These chemical reactions are catalyzed by enzymes. Oxidases, esterases, dehydrogenases, aminases are some of the enzymes found in the liver which accelerate the constantly occurring chemical reactions in this organ.

INDIVIDUAL FUNCTIONS

Certain functions are individual and cannot be grouped together. Among these are *blood volume regulation, heat formation, body temperature control* and *blood cell formation* (embryonic).

FACTORS INFLUENCING FUNCTION

The functions of the liver are influenced by physiological and pathological disturbances occurring elsewhere in the body. Changes in arterial and venous pressure, blood flow, anoxemia, hypercarbia and pyrexia may cause a depression of liver function. Toxic substances, either endogenous or exogenous, hormones and neurogenic stimuli, may influence the activity of the liver. The liver is peculiar in one respect. At times it appears to be very resistant to noxious agents while at other times it is so susceptible. Certain functions may be easily depressed by a given agent while others remain intact. This may be true even though the bulk of the parenchyma is destroyed. A slight change in physiological activity, a brief exposure to certain drugs, anoxemia, and other deleterious agents may initiate marked depression of one or more functions.

A noteworthy fact is that a substance which is altered by the liver does not necessarily harm the organ or depress its function while one that is not metabolized proves to be noxious. Chloroform, for example, is not altered chemically by the tissues but is capable of causing severe injury to the liver. Thiopental, on the other hand, is detoxified entirely by the liver, but causes no changes in function or damage to the parenchyma.

TESTS OF LIVER FUNCTION

Most tests of liver function have a *biochemical basis*. Many of the currently used tests are allied to each other in basic chemical behavior and may, therefore, be grouped together. These are as follows:

(1) Tests which measure the power of the liver to transform non-metabolizable

substances to forms which are easily assimilated by tissue cells. The *galactose tolerance test* assesses the ability of the liver to convert carbohydrates to glucose. Forty grams of galactose are administered orally. The urinary excretion is followed. Elimination of more than 4 or 5 grams unchanged indicates hepatic dysfunction. The *fructose tolerance test* does likewise. In this case the blood sugar curve is followed as is done in the glucose tolerance test. The ability of the liver to deaminize amino acids may be measured by studying the *tolerance to gelatin*. The rate of formation of urea and uric acid has been proposed as a test of function but is not practical clinically. Disturbances of liver function may sometimes be reflected by changes in lipoid metabolism. Elevations in blood cholesterol are *indicative of this. Blood* cholesterol levels are elevated in some types of hepatic disease.

(2) Tests which measure the efficacy of the liver to *excrete* or *secrete* endogenous substances. Examination of bile, since it contains both the secretions and excretions of the liver, yield useful data. This is not practical in man, however, because bile is not easily collected. Once bile passes into the intestinal tract it undergoes considerable alteration. Pigments are reduced to urobilin, and the salts are utilized in fat absorption or are reabsorbed. However, in animals, the gall bladder can be isolated and the bile can be collected quantitatively. Useful data have been obtained by this technique. Ordinarily traces of bile pigments are found in blood. When disturbances of liver function are severe, bile pigments may accumulate in blood in excess. Blood may then be analyzed directly for bilirubin content. The *icteric*

index is a colorimetric method for roughly estimating the concentration of bile pigments in serum. The color of serum is compared with a standard of aqueous potassium dichromate and the result is expressed in units. Five units or less is normal. *Von Bergmann and Eilbolt* devised a test based upon the capacity of the liver to excrete bile pigments. Sterile solutions of pure bilirubin are administered and the rate of disappearance from the blood stream is determined colorimetrically. The test is not practical because pure bilirubin is difficult to prepare in quantity.

The *Van den Bergh test* is a precise method used to detect and quantitatively estimate bilirubin. The bile pigments in blood are combined with protein and are, therefore, colloidal in nature. The protein is removed and the pigment is converted into a more soluble and stable form on passage through the liver cells. Bilirubin which has passed through the liver cells and has been divested of its protein produces an immediate pink color with the diazo reagent (nitrous oxide and sulphanilic acid). On the other hand, the colloidal form (that which is in blood which has not passed through liver cells) does not produce the color or does so after a period of time (delayed reaction) unless alcohol is added in which case the reaction is immediate. The latter reaction is often termed the *indirect* reaction, the former the *direct*. An indirect response usually indicates that liver cells are unable to excrete pigments and that formation is so rapid that an excess accumulates due to inability of the liver to keep pace with production. This happens when hemolysis occurs. In obstructive jaundice, the direct response is us-

ually obtained. This indicates that the pigments have been excreted by the liver cells but in some manner have found their way back into the blood. The protein freed of pigment is excreted by the kidney; the protein combined is not. The Van den Bergh test is useful in studies of severe liver disease or blood dyscrasias. Bilirubin and *biliveridin* are reduced to urobilin in the small intestine due to the action of bacteria. Urobilin is brown but may be reduced further to urobilinogin which is colorless. *Urobilinogin* is absorbed from the intestines and is either reconverted to bilirubin and biliveridin or passed into the urine unchanged. Increase of any urine urobilinogin indicates increased bile excretion by the liver.

All three tests, the icteric index, the Van den Bergh, and the von Bergmann measure the capacity of the liver to excrete *endogenous* substances.

(3) Tests which measure the capacity of the liver to excrete foreign or *exogenous* substances. The most useful of this type measures the ability of the liver to *eliminate dyes*. A number of dyes may be used but the type derived by halogenation of sulphthalein is used most frequently. The bromsulphthalein (B.S.P.) is the most widely-employed for hepatic function studies under anesthesia. The dye is injected intravenously after which specimens of blood are withdrawn at specified intervals, usually 15, 30 and 45 minutes. The dye in the serum is estimated colorimetrically. Clearance is delayed if hepatic function is disturbed. Five mgm. per kilo of body weight injected intravenously are usually cleared within fifteen minutes in man. These dyes are excreted into the bile. This test is used in anesthesia and surgical research because it excludes variable factors such as failure of a substance to be absorbed, as is the case with the galactose and fructose tolerance tests, or failure to be cleared by the kidney as is the case with the hippuric acid test described below.

(4) Tests based upon the *ability of the liver to detoxify* exogenous substances. The most widely employed test of this type is that devised by *Quick* which measures the capacity of the liver to *detoxify benzoic acid*. Benzoic acid is conjugated with the endogenously occurring amino acid, glycine, to form benzoyl glycine or hippuric acid. Six grams of sodium benzoate are taken orally or are injected intravenously. Hourly urine specimens are collected over a period of four hours. Three grams of benzoic, in the form of hippuric acid, are usually excreted by a normal adult liver in this time interval. This test is influenced by changes in urinary excretion or intestinal absorption. It, therefore, yielded less satisfactory data for anesthesia research than some of the others. The uncertainties due to variabilities in renal clearance may be averted by using paramino benzoic acid. This substance is conjugated to paraminohippurate which may be determined colorimetrically in a sample of blood collected one hour after the administration of a test dose of the metabolite.

(5) Tests based upon the concentration and the chemical nature of certain plasma proteins. These tests indicate the liver's capacity to synthesize circulating proteins. Among these are those necessary for coagulation, such as fibrinogen and prothrombin. The *prothrombin time*, for example, is a very sensitive test of liver function because it indicates the liver's ability to form prothrombin. This test cannot be used when biliary ob-

struction is present. An adequate vitamin K concentration in the liver is not assured in these circumstances. Vitamin K is necessary for the formation of prothrombin. It is not absorbed if bile is absent in the intestine. Plasma drawn from the patient is added to a mixture of specially prepared thromboplastin and iodized calcium. Clotting occurs promptly if prothrombin levels in the patient's plasma are normal. Clotting time is delayed if there is a decrease in circulating prothrombin. The test is not positive in many cases until a graph based upon normal values is used to calculate the prothrombin time.

The liver is the chief site for the synthesis of plasma albumins and globulins. Plasma albumin levels may be depleted due to failure of synthesis of the proteins or to unreplaced loss through kidneys or the vascular bed. Abnormal proteins may also form. The absence of the protective action of albumin or the alterations in gamma globulins due to hepatocellular destruction causes flocculation of emulsions of cephalin and other reagents. A barbital buffered supersaturated solution of *thymol* becomes turbid when mixed with serum from a patient with liver disease. The Takata-Ara test, which is no longer used, is based upon the fact that increased concentration of abnormal globulins in the serum give flocculation responses not given by normal proteins. The *zinc turbidity* test depends upon the low solubility of zinc compounds of gamma globulin in solution. *Hanger's test* depends upon the ability of serum of patients with hepatocellular disease to flocculate *cephalin-cholesterol* emulsions. The intensity of the reaction is proportional to the extent of the disease.

(5) Tests based upon the presence of

hepatic enzymes in plasma. *Alkaline phosphatase* is normally excreted in large amounts by the liver into the bile. High blood levels indicate failure of the enzyme to pass into the bile. This may result from impaired hepatic activity. Considered alone the test is of no value. When considered with other tests of liver function a high level may be significant. *Transaminase* activity is high in patients with acute hepatic cell injury. Elevations may also be due to changes elsewhere. Decreased blood flow, elevations in central venous pressure, anoxia, hypercarbia, epinephrine release, the degree of hydration, electrolyte balance and other factors in the preoperative state and during operation may induce changes. These changes are not specific for a drug. Instead they are due to secondary influences precipitated by the drug. It is not always possible to exclude these factors in evaluating laboratory and clinical data. Results in operated patients are variable and are influenced to a large extent by the type and duration of operation, the nature of the surgical disease and any co-existing disease. There is mounting evidence that liver impairment after operation is unrelated to the type of agent used for anesthesia, but that it is associated with the preoperative status of the patient and the extent of the surgical procedure. The most pronounced impairment occurs in patients of questionable preoperative risk and who undergo formidable and extensive surgical operations. Nonetheless, the data obtained under controlled conditions continue to remain of interest.

TESTS OF FUNCTION DURING ANESTHESIA USING DYES

The bromsulphthalein (B.S.P.) test has been employed extensively in

of hepatic function during and following anesthesia in both animals and man. Bourne and his associates and Coleman were among the early investigators to employ the test for anesthesia research. Others since then have continued to use the test to study injury due to halogenated hydrocarbons, hepatitis, and other liver diseases. The test is positive in other clinical conditions also. The test may be significant if other sources of protein destruction may be excluded. Serum *cholinesterase* activity likewise may be used as an index of hepatic activity since this enzyme is also elaborated by the liver.

Numerous other tests of liver function have been proposed. Each has its advantages and limitations. However, they are not relevant to this discussion and cannot be included here.

ANESTHESIA AND LIVER FUNCTION

Innumerable reports have appeared over the years in the medical literature concerning the changes in function during anesthesia caused by various single drugs or drug combinations. The earlier reports summarized data using dye excretion tests with single agents. More recent reports include data obtained using multiple agents and a battery of tests in which four or five functions are determined simultaneously. It was supposed at first that derangements in function were largely due to the effect of the drug upon the hepatic cells themselves. The thinking has shifted in recent years. It is now believed that the effects of anesthesia upon the liver are secondary to changes in other organ systems remote from the liver. The changes in the liver are merely secondary. Of the *major anesthetic agents,* the volatile liquids (ether and chloroform) markedly impair the ability of liver cells to clear

this dye from the blood. The degree of impairment varies with the duration and depth of anesthesia. In dogs, *chloroform,* for even as short a period as a half hour, produces impairment of excretion of the dye for as long as eight days. *Ether* in dogs produces an impairment in excretion which disappears the next day. *Ethylene* and *nitrous oxide* (without anoxia) and *cyclopropane* do not influence clearance time in either dogs or man. Repeated administration of cyclopropane does not change the capacity of the organ to excrete the dye in dogs. Anesthesia complicated by *anoxemia* or hypercarbia markedly diminishes the capacity of the liver to excrete the dye. Recovery of function is delayed for longer periods if anesthesia is complicated by anoxia. In operative man, Coleman noted an impairment of excretion of the dye for several days. In half the patients anesthetized with ether the impairment persisted for as long as seven days. Coleman also reported a delay in dye excretion following nitrous oxide anesthesia. Satisfactory anesthesia with nitrous oxide as the sole agent in man is usually obtained only with some degree of anoxia. Thus, the effects of anoxia cannot be excluded from these studies. *Divinyl ether* does not alter the capacity of the liver to excrete the dye unless anesthesia is complicated by anoxemia. Similar results have been obtained using ethyl vinyl ether and trifluorethyl vinyl ether. Halothane (Fluothane) suppresses dye excretion to the same extent as ether. Impairment of dye excretion follows the use of *trichlorethylene* in surgical depths. The *halogenated hydrocarbons* as a class are hepatotoxic and cause variable suppression of hepatic function. Histologically discernible hepatocellular changes may follow. Dye excretion is

not seriously impaired in subjects undergoing surgery anesthetized with spinal anesthesia. Spinal anesthesia, epidural block and other forms of regional anesthesia cause no impairment in function unless hypotension develops which is not corrected. *Local anesthesia* (infiltration) likewise causes no change in bromsulphthalein elimination in operated man. Dye excretion may be impaired from three to seven days after deliberately inducing hypotension with high spinal anesthesia or a ganglionic blocking agent. Dye excretion is impaired after hypothermia if a hypotension occurs.

Non-volatile drugs used for premedication or basal narcosis, as a rule, do not affect dye elimination unless they cause hypoventilation or hypotension. Basal narcosis with *thiopental* causes no impairment in dye excretion unless large doses are used and prolonged respiratory or circulatory depression occurs. Results using other ultrashort acting barbiturates, such as thiamylal or hexobarbital are similar to those with thiopental.

Morphine causes an impairment in dye excretion of variable duration depending upon the degree of depression. Barbiturates in therapeutic amounts have little appreciable effect upon the ability of the liver to excrete dyes. *Paraldehyde* decreases the capacity of the liver to excrete dyes. *Tribromethanol* in basal narcotic doses causes an impairment in dye excretion which does not return to normal for as long as seven days. Adjunctive drugs, such as *atropine, scopolamine,* the muscle relaxants and respiratory stimulants do not influence dye excretion.

Total body hypothermia does not in itself cause damage to the liver. However the general chemical reactions carried on by the liver are slowed down in proportion to the decrease in temperature. Detoxification of drugs proceeds at a decreased rate. There appears also to be a greater susceptibility to drugs which are ordinarily toxic to the liver.

ANESTHESIA AND SECRETION OF BILE

Molitor studied the effect of various anesthetics upon *bile secretion* in rabbits by isolating the gall bladder and collecting the bile secreted. The bile was reinjected into the duodenum in order to disturb circulation of bile as little as possible. Secretion was depressed when the chloroform was inhaled with air. *Chloroform* inhaled with oxygen produced a less-pronounced effect. Low concentrations of inhaled *ethyl ether* stimulate bile flow. Deeper ether anesthesia caused the flow to approach that of unanesthetized animals. *Vinyl ether* did not alter bile flow curves. *Nitrous oxide* with 20% oxygen produced no change. However, if anesthesia was accompanied by anoxia a marked fall in secretion occurred *Anoxemia* induced by 100% nitrous oxide completely inhibited flow of bile. *Ethylene* with adequate oxygenation produced no change. *Cyclopropane* with 75% oxygen produced an increase in bile secretion. Changes in the composition of the bile were not noted. Mann and his co-workers performed similar experiments using ether but obtained somewhat different results. Ether inhibited bile flow in their studies.

Tribromethanol causes an increased bile flow. The composition of the bile, likewise, is changed. Less bilirubin was present per unit volume of bile, but the total bilirubin excretion was the same as in unanesthetized controls. Both the relative and absolute concentrations of bile salts were decreased during tribromethanol narcosis.

Chloroform anesthesia is accompanied by a transient rise of bilirubin in blood and of urobilin in urine. These pigments persist in abnormal amounts for several days. In prolonged chloroform anesthesia in dogs, the icteric index also may rise. Starvation, anoxia, and preoperative feeding of large quantities of fats predispose to hepatic damage with *chloroform*. Volatilizing the chloroform with oxygen and the preoperative feeding of glucose and xanthines minimizes damage to liver in experiments on animals anesthetized with chloroform.

ANESTHESIA AND SYNTHETIC FUNCTIONS

The effects of anesthesia upon synthetic functions of the liver have been studied to a lesser extent than the dye excretory function. These tests are technically more difficult to perform than the dye excretion tests. Boyce and his associates and Schmidt and his co-workers studied hepatic function in operated man using the hippuric acid test. Boyce noted a decrease in synthesizing power in almost half of the subjects anesthetized with spinal anesthesia. Schmidt obtained no change of function using *spinal anesthesia* unless a hypotension complicated the procedure. Presumably the diminished capacity to conjugate benzoic acid following spinal anesthesia was due to anoxemia or diminished blood flow associated with the hypotension characteristic of this procedure. *Ether* and *ethylene* also produced similar but less intense changes. *Ether* produces a decrease in function with the test in all subjects studied in Schmidt's series. Function was depressed approximately 35% but returned to normal within a week. *Tribromethanol* caused reduction in function from 5% to 30%. No changes were noted in this test during local anesthesia in subjects to whom *morphine* or *amytal* was administered for sedation.

GLYCOGEN STORAGE

The capacity for *storage of glycogen* by the liver is also disturbed by anesthesia. *Chloroform* and *ether* anesthesia quickly deplete its glycogen stores by causing glycogenolysis. The response is due to the release of epinephrine or sympathetic stimulation. A concomitant elevation in blood sugar occurs. Clinically insignificant elevations in blood sugar occur with cyclopropane, ethylene, nitrous oxide, vinyl ether, halothane, thiopental, spinal and regional anesthesia. General, well-defined rises in blood sugar occur if anoxia or hypoventilation complicate anesthesia. The liver under ordinary circumstances converts lactic acid to glycogen. During anesthesia, particularly with chloroform and ether or during anoxemia, the organ does not seem to be able to accomplish this. Liver glycogen is depleted during morphine narcosis and in some cases during barbiturate narcosis when respiration is depressed.

PROTEIN METABOLISM

The ability of the liver to form urea is not, as a rule, hindered until considerable damage to or destruction of parenchyma occurs. During *ether* anesthesia, *urea formation* is not decreased. In some cases it is increased.

BLOOD COAGULATION AND LIVER FUNCTION

Tests of liver function dependent upon the ease of coagulation of blood yield little data of practical significance. Plasma fibrinogen is reduced by hepatitis

due to chloroform, carbon tetrachloride and other halogenated compounds. *Coagulation* time is slightly prolonged during *chloroform* but is shortened during *ether, ethylene, avertin,* and *nitrous oxide* anesthesia. No change in coagulation time occurs during surgical anesthesia with *cyclopropane.* However, these changes are so slight that they are of little clinical significance. Changes in coagulation time are not necessarily the result of depression of hepatic function. More likely they are due to changes in composition and reaction of tissues and blood. *Prothrombin time* is significantly prolonged after *chloroform* anesthesia. Other anesthetic agents appear to influence prothrombin time little if at all. Even when prothrombin is deficient preoperatively no further change in prothrombin time is noted if such patients are anesthetized with the currently employed agents.

HISTOLOGICAL CHANGES DUE TO ANESTHETIC DRUGS

Derangements in the liver function are not necessarily associated with discernible histological changes in the liver. A marked degree of functional impairment may exist and yet the cells appear to be normal on histological examination. Some drugs, however, are notorious for their effects on the liver; notably the halogenated hydrocarbons.

Halogenated aliphatic hydrocarbons are hepatotoxic in varying degrees. The most toxic appear to be the single carbon chlorinated and brominated derivatives. Both chloroform and carbon tetrachloride may initiate histological changes and symptoms of *hepatitis.* The response is delayed for several days after anesthesia. The microscopic changes with chloroform may appear as early as six

hours. The exact mechanism which causes the hepatitis *is not known.* However, vasospasm appears to be the most probable cause. Other *halogenated hydrocarbons* may produce the same effect but to a lesser degree. The possibility that the drug interacts with substances in the tissues to form compounds toxic to the hepatic cells has been suggested but never proved. The cells in the center of the lobule are the most susceptible in chloroform poisoning. Clinical signs of severe hepatic insufficiency develop. Jaundice, bile in the urine, increased serum bilirubin, increased icteric index and tendency to hemorrhage are all present. Lipoid, carbohydrate, and nitrogen metabolism are disturbed. Fat accumulates in the liver. Glycogen storage is impaired. Galactose and fructose tolerance tests are impaired. The capacity to form urea is lost. The deaminization of amino acids does not occur. Therefore, these acids increase in blood and appear in urine. Capacity to form uric acid is disturbed. Urea formation may not be disturbed until a very large part of the liver is damaged, however. The hepatitis appears to be less frequent with unsaturated halogenated hydrocarbons. The histological changes characteristic of chloroform have not been observed after the use of halothane.

Divinyl ether in repeated administrations also causes a central necrosis of the liver lobule in dogs. Single administrations do not do so unless the anesthetic is complicated by anoxia. Halogenated alcohols and aldehydes, unlike the halogenated hydrocarbons do not cause histological changes in the liver. During total body hyperthermia the liver appears to be more susceptible to toxic effects of drugs. Vinyl ether causes a definite central necrosis.

CONCLUSIONS

It seems apparent that more than one function is disturbed by anesthesia and that the varying degrees of impairment of function which are noted are difficult to assess from a clinical standpoint. The impairment is most likely due to a secondary and possibly remote cause and not to the influence of the drug on the hepatic cells themselves. The changes in function vary little among the major agents, such as ether, fluothane, cyclo-propane and so on. Function is influenced to a large extent by anesthetic techniques, preoperative status of the patient and the magnitude, duration and severity of the surgical procedure. Heretofore changes in hepatic function and their direct relationship to the effect of anesthetic drugs per se have been over-emphasized. The drugs are now believed to play a secondary role in causing the dysfunction. Dysfunction is not related to the liver's rôle in detoxification of a drug.

Effects of Anesthesia Upon Formation and Composition of Urine

STRUCTURE AND FUNCTION OF THE NEPHRON

THE FUNCTION OF THE KIDNEY is to maintain the composition of the blood constant to suit the body needs. The interchange between the intercellular fluid and blood tends to oppose this constancy of blood composition. The normal human kidney is composed of a million or more *nephric units called nephrons*. Each of these units is composed of a *glomerulus* and a *tubule*. The glomerulus and the tubule are supplied with the same *arterial blood*. An *afferent arteriole* first carries the blood to the glomerulus. An *efferent arteriole* then carries this arterial blood from the glomerulus to the tubule. The glomerulus *filters* crystalloids and small sized colloidal particles while the tubules *secrete* various substances and *absorb* others. Each portion of the unit functions separately. The blood flow through the nephron is fairly constant. It is, however, subject to variations caused by autonomic nervous system effects, local constrictor and dilator effects, hormones, and anoxia. Epinephrine constricts the afferent vessels to the glomerulus and causes a decrease in filtration rate. The *antidiuretic hormone* secreted by the posterior lobe of the pituitary gland increases tubular reabsorption of water and thereby decreases the volume of urine formed. Anoxia increases permeability of the renal epithelium. Reflex vasoconstriction elevates systemic blood pressure and increases blood flow through the kidney, thereby increasing the filtration rate. The *colloids* (serum proteins) of blood are ordinarily impervious to the renal epithelium and do not ordinarily pass into the urine. Alterations in blood volume accompanied by changes in blood composition may retard or increase the rate of urine formation, depending upon the situations which develop.

COMPOSITION OF THE URINE

Urine may be defined as a complex aqueous solution of organic and inorganic substances elaborated by the kidney. Urine is the chief avenue for elimination of end products of protein catabolism, inorganic acids and salts, end products of detoxified drugs, hormones and excess water. The kidney plays an important role in maintaining blood pH at the proper level. This organ handles the elimination of acids, particularly the non-volatile ones, since acidic products are the main products of metabolic activity. The reaction of the urine ordinarily is *acid*. However, the kidney can form an alkaline urine if blood contains an excess of base. The urine may become

alkaline in cases of excessive fluid loss, following hyperventilation with loss of carbon dioxide or in cases of excessive vomiting which causes loss of hydrochloric acid from the stomach. The acid products are excreted as salts. Basic disodium hydrogen phosphate of plasma is converted to acid monosodium dihydrogen phosphate which is the main inorganic acid product of urine. The kidney *helps conserve base* in cases of excessive acid formation. It does this by forming ammonia from urea or amino acids. This neutralizes acids and forms ammonium salts which pass into the urine. No mechanism of similar nature exists to conserve acid since excess base formation is unusual in metabolism.

The *total urinary solids* may amount to 50 to 60 gms. in 24 hours (volume about 1500 ml.). Organic constituents comprise 30 to 50 gms. of this total. The remaining constituents are inorganic substances. Urea, uric acid, creatine, creatinine, ethereal sulphates, hippuric and oxalic acids, natural sulphur compounds, aromatic acids, lactic acid, phenaceturic, urocanic, phosphuronic glycerphosphoric acids, pigments, purine bases, and enzymes (trypsin and amylopsin) are the usual organic constituents.

Inorganic substances are chiefly electrolytes. Chloride, sulphate, phosphate, carbonate, fluoride, nitrate, and silicate are the anions consistently found. Sodium, potassium, calcium, magnesium, and iron are the important cations. Knowledge of the exact concentrations of these constituents in normal urine is of little clinical value because diet, metabolic processes in the body, and other factors *cause day to day variation* in composition.

Abnormal substances pass into the urine. Detection and quantitative esti-

mation of these are of extreme importance in diagnosis and treatment of disease. Glucose, ketone bodies, proteins, amino acids, bile salts, bile pigments, blood, and other substances are some of the constituents which may be evidence of disease. The kidney can filter, excrete, and reabsorb crystalloids, some colloids and water. *Some substances* which pass into the glomerular filtrate are completely reabsorbed by the tubules (glucose). If an excess is present in the plasma this *reabsorption is complete up to a certain* limit known as the renal *threshold*. Beyond this limit the reabsorption is no longer complete and the substance then appears in the urine. *Substances of no* particular value to the body have no threshold and are not reabsorbed. Some drugs are reabsorbed by the kidney tubules. Barbiturates, for example, have a low renal threshold.

RENAL FUNCTION TESTS

Available Methods

There is no single test which specifically indicates how the kidney is functioning. The routine urine analysis, the blood urea and the non-protein nitrogen determination are non-specific tests which yield information of questionable value, unless gross deviations from normal are present. Besides such deviations may be due to extra-renal factors rather than renal. There is no way of distinguishing which is which. Alterations in nitrogen intake, water and electrolyte balance may have considerable influence on the results of these tests. Syndromes accompanied by anorexia, vomiting, diarrhea or excessive sweating may have profound influence on the urea and total non-protein nitrogen blood levels.

There is no simple way of determining

how the nephron, considered as a single unit, is functioning. Present day methods of studying renal function rely upon a battery of tests, each one of which measures the performance of a certain portion of the nephron. The rate of glomerular filtration, renal blood flow, absorptive capacity of the proximal tubule, tubular secretion, and reabsorption by the distal tubules are determined individually. Conclusions are then drawn from the composite data obtained from these tests.

GLOMERULAR FILTRATION

Inulin Clearance

The rate of glomerular filtration may be determined quite accurately by measuring the clearance of inulin from the blood. Inulin is a polysaccharide which passes freely through the glomerular membrane. It is ideal for the purpose because its molecule is small and it is not metabolized in the body. Besides it is neither secreted nor reabsorbed by the tubules. The quantity filtered into the urine per minute divided by the plasma concentration is an index of the rate of filtration. In order to perform the test simultaneous blood and urine inulin concentrations must be obtained. The amount of inulin removed from the plasma in a unit of time is referred to as *inulin clearance.* The term clearance is a general one which is applicable to a variety of substances. The volume of blood or plasma which appears to be cleared of a particular substance in a unit of time is called *clearance.* The value is expressed in ml. of blood or plasma completely cleared of the substance per minute. It is computed by multiplying the volume of urine formed in a unit of time by the concentration of

the substance in the urine and dividing this result by the plasma concentration $(u \times v \div p)$.

CREATININE CLEARANCE

Creatinine is normally eliminated by the glomeruli. The clearance of creatinine is similar to that of inulin. *Creatinine clearance* may also be used to measure glomerular filtration, since it is neither absorbed or secreted by the tubules. The mean normal inulin and creatinine clearances (glomerular filtration) are between 124 and 130 ml. per minute.

UREA CLEARANCE

The clearance of urea is also used as an index of glomerular function. The *urea clearance* test was introduced by Möller, McIntosh and Van Slyke. It is less sensitive than the inulin clearance because urea is partly reabsorbed by the tubules. The test, therefore, is of a semi-quantitative nature. However, within certain limits it is reasonably accurate and, therefore, it is suitable for clinical use. Besides it is more easily performed than the inulin clearance test. The inulin clearance, however, is preferred for clinical investigation and for studies in basic physiology and pharmacology.

The total amount of urea excreted into the urine during a given time interval is determined by chemical analysis of blood and urine. The difference in concentration of urea in the blood at the beginning and at the end of the test is used to compute the volume of blood which is cleared of urea in that time is calculated. Normally 60 to 74 ml. of blood are cleared of urea per minute. The quantity of urea cleared is usually expressed in terms of weight of urea

cleared per meter of body area, as are most blood flow studies. Urea is filtered through the glomerulus at the same rate as inulin. However, the test indicates that a larger volume of blood has been cleared than actually is due to the fact that urea is not only filtered, but is also partly reabsorbed by the tubules. In order to eliminate the error introduced by the reabsorbed urea and obtain an approximately true filtration rate the urea cleared is multiplied by the factor 1.2. The reabsorption of urea is reduced somewhat when the urine flow is above 1.5 ml. per minute. A progressive increase in urea clearance occurs as the urine flow increases. Urea clearance, therefore, depends upon urine volume. This is subject to variations. However, this effect is relatively unimportant when the flow of urine is between 1.5 and 12 ml. per minute. When the urine flow falls below 1.5 ml. per minute the urea clearance is not a reliable index of the ability of the kidney to clear urea. Extra renal factors such as dehydration, reduced filtration rate and reflex vasoconstriction may come into play. Clearance, as Homer Smith and his associates define the concept, should be entirely divorced from urine volume.

RENAL BLOOD FLOW

Renal blood flow is determined by measuring the rate of clearance of paramino hippuric acid or diodrast from the plasma. These substances, if present in dilute concentrations, are completely removed by one circulation of the arterial blood through the kidney. Therefore, their clearance is identical with the rate of blood flow through the kidney. The mean normal renal blood flow measured by the hippurate clearance is 1200 ml. per minute.

TUBULAR EXCRETION

P.S.P. TEST

Another substance often used to determine renal function, and to a certain extent renal blood flow, is the dye phenolsulfonphthalein (P.S.P.). Most of this dye is removed by one passage through the kidney. The elimination of P.S.P. is mainly by tubular excretion. The volume of urine formed is measured and the amount of dye eliminated is determined colorimetrically. However, the quantity of dye for the test is usually insufficient to give a plasma concentration of sufficient magnitude to bring about a maximal tubular excretion. The tubular tissue may be slightly damaged, yet it clears the dye easily. Unless the period of collection of urine is brief, such impairment of function is unnoticed. The urine specimen obtained fifteen minutes after injection of the dye yields information of greatest value. The maximum concentration of dye is present in plasma at this time. The excretory power of the tubule, therefore, is closer to its maximum. Since the excretion of the dye is affected by both renal blood flow and tubular secretion, a reduction in output may indicate impairment of tubular function and blood flow. Ordinarily this test is performed in a number of ways. Specimens of urine are usually collected at one hour and two hour intervals after the intramuscular injection of 6 mgm. of the dye. Normally 40 to 60% of the injected dye is recovered during the first hour and an additional 20 to 25% may be recovered during the second hour. The maximum recovered totals 60 to 85%. The test as ordinarily used clinically gives very little useful data concerning renal function.

DIODRAST METHOD

Tubular excretion is best measured by

raising the plasma concentration of paramino hippuric acid or iodopyracet (diodrast) above the level at which it is completely cleared by one circulation through the nephron. The tubular excretory mechanism then becomes totally activated and a substance is excreted at a maximal rate. The amount in the urine in a given time is determined. By so doing the maximal tubular excretory capacity is reached and this is assumed to represent the amount of actively functioning tubular tissue.

TUBULAR REABSORPTION

The primary function of the *proximal tubule* is to reabsorb substances necessary to the body which pass through the glomerular membrane into the filtrate. Glucose is one such substance. The *distal tubules* absorb water. It is this part of the nephron which concentrates the urine. Reabsorption is measured by the use of glucose. The plasma glucose level is raised above the threshold value by a constant infusion. The glucose passes through the glomeruli and is reabsorbed by the proximal tubules. Glucose appears in the urine when a plasma glucose level of 280 mgm. or more per 100 ml. has been obtained. This indicates that the tubular absorptive capacity has been exceeded. The mean normal value for the maximal reabsorption capacity of the tubules, measured by the glucose reabsorption technique, is 400 mgm. per minute.

CONCENTRATING AND DILUTING POWER

The kidney conserves water or eliminates it according to the body needs. Thus, the total solids per unit volume of urine is subject to considerable variation, depending upon the body need for water. A concentrated urine which is hypertonic in relationship to the blood may be elaborated. On the other hand if there is ample supply or an excess of water one which is hypotonic may be secreted. The total urinary solids per unit volume of urine may serve as an index of the concentrating and diluting power of the kidney. This may be ascertained by determining the specific gravity. The maximal concentrating capacity of the kidney is an index of its ability to excrete a maximum weight of solids in the smallest amount of water. Loss of concentrating power is indicated by an unvarying specific gravity ranging a little above or below 1.010. This is the specific gravity of protein free plasma. In addition, the day and night output of urine become the same. Ordinarily it is less at night. Ordinarily kidneys can elaborate a urine having a specific gravity as high as 1.024. If an excess of water is ingested it may elaborate one which is so dilute that its specific gravity falls as low as 1.001. Urine concentration and dilution tests measure the ability of the distal tubule to absorb water. Various concentration and dilution tests have been introduced. The *Mosenthal test is* an example of one which measures the ability of the kidney to form a concentrated urine. The test of *Volhard and Farr* measures the capacity of the kidney to form both a dilute and concentrated urine. These are simply dilution and concentration tests designed to detect gross impairment of function in the absence of extra renal disturbances which may secondarily affect urine formation. As a rule, measure of the diluting power of the kidney is of little help in evaluating the status of the kidney function, since numerous extra renal factors may cause it to vary.

THE EFFECTS OF ANESTHESIA ON RENAL FUNCTION

INFLUENCE OF EXTRA RENAL FACTORS DURING ANESTHESIA

The subject matter concerning the effects of anesthesia on renal function is voluminous and appears in a confused state. In some reports conclusions have been drawn from data obtained by using a variety of tests, many of which are of a semi-quantitative nature capable of detecting only gross changes. Much of the published data has been obtained from uncontrolled experiments. Numerous factors, many of them extra renal, profoundly influence renal function during anesthesia. Anesthesia causes a multitude of physiological changes. Anesthesia may cause changes in blood flow, blood volume, changes in capillary permeability, a release of hormones of the adrenal and the pituitary, changes in osmotic pressure, disturbances of the electrolyte pattern, a migration of water from or into the intracellular spaces, changes in environmental temperature which influence fluid loss, decreases in absorption from the gastrointestinal tract and changes in autonomic reflex activity all of which influence renal function. Thus, when interpreting results it *is difficult to determine whether or not* the changes in renal function are primary and due to a direct action of the drug on the kidney or if they are secondary to other changes caused by anesthesia. Obtaining a true picture would involve a study of the effects of the drug upon each component of the nephron and an exclusion of all extraneous factors. This *is* difficult if not impossible. Studies of simultaneous measurement of glomerular filtration, tubular reabsorption, tubular secretion and renal blood flow which have been made during anesthesia are few. The most extensive studies utilizing these techniques are those of Habiff and his associates. These are discussed further on.

EFFECTS OF ANESTHETICS

In spite of the lack of systemic and controlled studies, a general trend can be detected in the majority of the studies reported. It is consistently found that general anesthesia causes a reduction in urine formation. Furthermore, the disturbances, whatever the cause may be, disappear and there is an apparent return to the usual physiologic level after anesthesia. These effects appear to be due to extra renal disturbances rather than a direct effect upon the kidney. Damage to the tissue of the kidney itself seldom occurs. The responses are stereotyped for all general anesthetics. Apparently an intrarenal vasoconstriction occurs with all general anesthetics. This is associated with a fall in glomerular filtration, a decrease in concentrating power, and alteration of excretion of electrolytes and water. The reabsorption of electrolytes and water by the renal tubular epithelium appears to be increased relatively speaking. Operation, in the absence of shock, hemorrhage and other complicating factors, has little effect on renal function Most of the changes appear to be due to the influence of the anesthetic itself.

Ether anesthesia, as most observers have noted, upsets renal function and causes an oliguria followed by a compensatory polyuria. Pringle was the first to observe a decreased urinary output during ether anesthesia in man. Studies

on the excretion of phenosulfonphthalein in operated humans anesthetized during ether anesthesia revealed a decrease in the capacity to excrete the dye. Dye excretion returned to normal within 20 to 48 hours. Orth and Stutzman in a post anesthetic follow up after the use of ether, using the urea clearance test as a measure of kidney function in dogs, noted no variation of any significance over a period of 8 months from the preanesthetic control levels. Water diuresis in the immediate postanesthetic period was normal. Habiff and his co-workers noted a 40% reduction in glomerular filtration and a decrease of 54% in renal plasma flow in humans. Similar observations were noted by Burnette and his associates. There appears to be increased reabsorption of water, sodium and chloride during ether anesthesia.

Chloroform also causes a progressive decrease in urinary output both in man and animals. Orth and Stutzman using the urea clearance test as a measure of function noted that anesthesia given for periods of one hour or more in dogs caused no variation of any significance from the preanesthetic control levels. The dogs were observed over a period of 8 months.

Little data is available on the effects of *nitrous oxide* on renal function since this drug is seldom used as the sole agent. When used alone anesthesia is usually accompanied by anoxia. Axelrod and Pitts induced anoxia with oxygen poor mixtures of nitrous oxide and studied renal function. No significant effects were noted on renal tubular function or glomerular filtration in dogs and humans. Data on the influence of anoxia on renal function during anesthesia are meagre. The effects of the combination of *sodium*

thiopental and *nitrous oxide* on glomerular filtration, renal blood flow and tubular function were similar to those observed for ether. A diminution in glomerular filtration and a decrease in renal blood flow occurs.

Cyclopropane anesthesia, like ether, is accompanied by suppression of urine formation. During recovery a compensatory polyuria follows. The results of most workers are in agreement in this regard. The mechanism causing the change is assumed to be similar to that noted during ether anesthesia, i.e., a renal vasoconstriction. Orth and his co-workers using the same techniques mentioned in their studies on ether and chloroform indicate no variation of urea clearance for an 8 months' period after a one hour period of anesthesia.

Little change in phenolsulfonphthalein excretion during *ethylene* anesthesia was observed by Luckhardt and Lewis. Data using other techniques is not available.

Tribromethanol causes a suppression of urine formation. Oliguria and often anuria is observed in dogs. A compensatory polyuria follows recovery. The anuria seen in animals does not occur in man. However, oliguria does occur. The effects of barbiturates are variable. Much depends upon the type of barbiturate studied and the depth of narcosis produced. Thiopental causes a suppression in output. Corcoran and Page observed that *pentobarbital sodium* (30 mgm. per kilogram) in dogs did not significantly alter glomerular filtration or renal plasma flow. Larger doses of barbiturates cause a diminution of urine flow. Possibly some of this is due to the release of the antidiuretic hormone. The *narcotics,* meperidine and morphine,

cause suppression of output as do the general anesthetics. Meperidine in 100 mgm. doses causes the glomerular filtration rate to drop in man from 20–45% and the renal plasma flow to fall 25–50%. Morphine in 10 mgm. doses causes similar but less striking responses.

Smith and his co-workers found no significant changes in inulin and diodrast clearance during *spinal anesthesia* in unoperated and unpremedicated man. However, if spinal anesthesia is supplemented with general anesthesia the results are quite different. Habiff, Bradley and others observed that *high spinal anesthesia* supplemented with cyclopropane, ether, thiopental or nitrous oxide and oxygen produced the same changes in renal function as would be caused by these agents used without spinal anesthesia. Presumably, denervating the kidney with spinal anesthesia does not alter the vascular changes induced by general anesthetics on the kidney. Orth observed a decrease in urea clearance after daily repeated administrations of *vinyl ether* to dogs. Single administrations did not cause any change. Data following a single administration in man are not available. Miles and his co-workers noted that *deliberately induced hypotension* using ganglionic blocking agents, such as hexamethonium, during ether and cyclopropane anesthesia causes no further change in the function of the kidney beyond that caused by the anesthetic. However, some renal damage, in spite of such findings, does occur and is one of the complications. Proteinuria, casts and red cells are found frequently in the urine postoperatively. During *hypothermia* (temp. 24°C.) Churchill-Davidson observed a diminution in renal

function which was ascribed to a decrease in blood flow.

ROLE OF THE ANTIDIURETIC HORMONE

The antidiuretic hormone which is liberated by the posterior lobe of the pituitary regulates the absorption of water by the renal tubules. This hormone is said to play a dominant role in the diminished urine flow caused by anesthetics. Presumably, anesthetics cause an increase in the output of this hormone. However, this point is debatable. In dogs subjected to section of the pituitary followed by diabetes insipidus, cyclopropane, ether, morphine and pentobarbital continued to cause antidiuresis. The effect of the antidiuretic hormone, therefore, does not account entirely for the diminished urinary output during general anesthesia with these drugs.

HISTOLOGICAL CHANGES CAUSED BY ANESTHESIA

The commonly used anesthetics are not toxic to renal tissues. Histologic changes in the kidney parenchyma due specifically to anesthetic drugs do not occur, save after chloroform hepatitis. The possibility of lesions in the human kidney from vinyl ether has been suggested from experimental data observed in dogs after repeated administration of this drug daily for a week. However, the assumption that this occurs in the human kidney after a single administration of the drug is erroneous. Changes secondary to ischemia may follow hypotension during operation. These, however, can hardly be ascribed to the drugs used. Histologic changes are secondary.

EFFECTS OF ANESTHESIA UPON THE
COMPOSITION OF THE URINE

VOLUME

The composition of the urine varies widely after anesthesia. Variations in composition are not necessarily an index of diminished function. A factor of importance in such studies is the state of hydration of the patient prior to operation. This together with the other variable factors which influence renal function has profound influence on both the volume and composition of the urine.

REACTION

The urine is normally acid in reaction, the pH varying from 5.3 to 6. The postanesthetic acidity is usually increased, particularly in instances where anesthesia causes a shift of acid-base balance to the acid side. Ketone bodies are responsible for little of the acidity. Excretion of inorganic acids, acidic substances (phosphates) as well as non-volatile acids (lactic, phosphoric, acetic, oxalic and oxyluric) is decreased during *ether* anesthesia in the postanesthetic period in human subjects who have undergone operation. *Chloroform* anesthesia during operations on human subjects is accompanied by a fall in urinary phosphates. A rise usually occurs in the postanesthetic period. Basal narcosis with *Avertin* causes an increase in the output of phosphoric acid. Walton noted changes in phosphates in the urine after ethylene and amytal anesthesia. He observed no changes following the use of Avertin alone.

URINARY NITROGEN CONTENT

Urinary non-protein nitrogen decreases during anesthesia but increases during the recovery period with most anesthetic agents. Urinary ammonia is increased after *ether* anesthesia. In the immediate postoperative period water diuresis is normal following *ether, ethylene, tribromethanol* and most *barbiturate* anesthesia in dogs.

ELECTROLYTE CONTENT

In general the total output of electrolytes is diminished even though the concentration per unit volume is increased because of the reduced urinary output. Data on individual electrolytes and agents are meagre. Presumably there is an increase in tubular reabsorption of water, sodium and chloride. During *cyclopropane* anesthesia the output of sodium chloride is considerably reduced. The potassium content is variable. Similar findings occur with *ether* anesthesia. Friden and his co-workers noted that the kidney of the dog retains abnormal amounts of sodium due to increased tubular reabsorption when the peripheral venous pressure is elevated. It is obvious from the foregoing that data on this aspect of biochemistry are meagre and that any analysis of concentrations of urinary solids yields information of little clinical value.

PROTEINURIA

The renal epithelium ordinarily is impermeable to serum proteins. None, therefore, appears in the urine. After ether, chloroform and other types of anesthesia a transient albuminuria occurs in a variable percentage of patients. Casts and leukocytes may occasionally be found postoperatively after almost

any type of anesthesia. These are believed to be caused by factors other than anesthesia, such as dehydration or infection. Threshold substances such as glucose rarely appear in the urine as the result of anesthesia or operation, unless this drug has been infused in excess quantities.

PRODUCTS ARISING FROM ABNORMAL METABOLISM

Chloroform poisoning with hepatitis is accompanied by an increase in total uric acid of the urine suggesting increased protein catabolism (Marshall and Rowntree). Bile may also be excreted as well as glucose in this syndrome. Data of a positive nature is not available concerning other anesthetics.

EXCRETION OF DRUGS INTO THE URINE

Volatile anesthetics appear in the urine in traces. Non-volatile substances which pass from the body unchanged are excreted into the urine almost entirely. Some passes into the sweat, milk and feces. Detoxified drugs also pass into the urine. Tribromethanol, for example, is conjugated with glucuronic acid by the liver and the conjugated product is eliminated by the kidney into the urine. Pentobarbital, on the other hand, is metabolized completely in the body and none is found in the urine, save in overdosage. Both the unchanged drugs and detoxified products are retained when renal dysfunction is present. Animals with experimental nephritis produced by uranium sleep longer following the administration of barbital than do the controls. The renal excretion is prolonged when non-metabolized drugs ordinarily excreted by the kidney are administered if renal dysfunction is present.

HEMODIALYSIS—THE ARTIFICIAL KIDNEY

BASIC CONCEPT

The artificial kidney is an extra-corporeal hemodializing apparatus which is based upon the fact that plastic membranes are semi-permeable. The artificial kidney provides an imperfect substitute for diminished or absent glomerular filtration. None of the complex functions of the tubules can be taken over by the device. A portion of the nitrogenous metabolites are removed and levels of some electrolytes are restored to normal by the dialysis. The greatest amount of any substance removed is urea.

PRINCIPLE

The patient's blood enters the dializing apparatus by means of a canula inserted into an artery, usually the radial. The blood circulates through a cellophane tubing, which is immersed in a bath called the dializing fluid. The bath fluid is a mixture of electrolytes containing the following ions: potassium, sodium, chloride, bicarbonate, calcium and phosphate. The blood is forced through the tubing by means of a pump or by the tumbling effects of a drum upon which the tubing is wrapped. During the passage through the tubing the solutes are transferred across the cellophane membrane into the dializing fluid. The dialyzed blood passes the distal end of the tubing back into the body through a vein in the foot.

A number of models of the apparatus are available, all of which are based

upon the same basic principle. In the rotating drum type the membrane consists of a tube about 100 ft. long. This is first detoxified by prolonged boiling. It is then filled with the blood compatible with that of the patient. Coagulation of the blood is prevented by the injection of 100 mgm. of heparin at regular intervals.

USES

The kidney removes the substances with a small molecular diameter such as urea, uric acid, creatinine and other waste products from the blood. The concentration of non-protein nitrogen elements may be reduced to ½ of the initial values within a five hour period of dialysis. The concentration of potassium and other electrolytes tends to approach that of the bath fluid. One may, by adjusting the concentration of these ions in the bath fluid, correct any abnormal electrolyte pattern of the blood. Glucose (3%) is added to the bath fluid to prevent absorption of fluid by the body or to remove fluid from the tissues in cases complicated by edema. Dialysis is usually carried on for periods averaging five hours.

The artificial kidney is used for patients who have renal insufficiency of a reversible nature which is accompanied by anuria or oliguria and azotemia.

LIMITATIONS OF USES

The artificial kidney does not modify the histopathologic changes involved in renal insufficiency. It is, therefore, of little value in diseases characterized by irreversible changes in the kidney. Its only value is, therefore, in the management of abnormalities which result from *renal disease. Its uses should be directed primarily in the treatment of renal failure in which the pathological physiology of the condition depends, to a great extent, upon chemical abnormalities in the plasma.* The kidney has been employed with varying degrees of success for the treatment of overdosage from diffusible poisons, which are not nephrotoxic, such as barbiturates, bromides, salicylates and so on. Its value for massive barbiturate overdosage is a debatable subject. Its use is generally reserved as a measure of last resort in cases of severe intoxication. It may be indicated when specific renal toxins, *such as heavy metals and inorganic* acids have been taken inadvertently. It may be of benefit in renal failure due to the lower nephron syndrome following shock, severe trauma or the use of incompatible blood.

Effects of Anesthetic Drugs on Lipid and Nervous Tissues

CLASSIFICATION AND CHEMICAL NATURE OF LIPIDS

THE LIPID-CONTAINING TISSUES are of interest to the anesthetist because anesthetics are lipophilic. The uptake of anesthetics by these tissues is greater than by other tissues. The term *lipid* * is a broad and general one. It includes not only *fats* and *fat-like* substances but also associated substances. Lipids may be classified into the following groups:

(A) *Simple lipids.* In this category are (1) the plain fatty acids and glycerol esters of fatty acids and (2) the waxes. Waxes are esters of fatty acids and high molecular weight mono hydroxy aliphatic or aromatic alcohols. Spermaceti is an ester derived from cetyl alcohol and palmitic acid. Waxes are classed as (a) true waxes, (b) cholesterol esters, (c) vitamin A esters, and (d) vitamin D esters. True waxes are products of animal and vegetable origin in which the esters are composed of palmitic, stearic, oleic or other higher fatty acid esters of cetyl alcohol.

(B) *Compound lipids.* In this category are glycerol esters of fatty acids which upon hydrolysis yield some other substance in addition to fatty acids and glycerol. They are also known as conjugate lipids. This group is subdivided in-

*Synonymous with the older term *lipoid* and also the terms *lipide* and *lipin*.

to (a) phospholipids, (b) glycolipids, and (c) sulpholipids. Phospholipids yield phosphoric acid, glycerol, and nitrogenous bases, such as choline or ethanol amine, upon hydrolysis. Lecithins, cephalins, and sphingomyelins are examples of members of this group. Glycolipids when hydrolyzed yield fatty acids, a carbohydrate usually galactose) and a nitrogenous base, syphyngosine. Glycolipids contain nitrogen but no phosphoric acid. They are frequently referred to as *cerebrosides* because they are abundant in nerve tissue. Phrenosin and kerasin are well-known examples of cerebrosides. The structure of sulpholipids is not well-defined. They yield sulphuric acid and nitrogenous compounds upon hydrolysis. They are prominent in nerve tissue also.

(C) *Derived Lipids.* In this category are lipids obtained by hydrolysis of compounds listed under groups A and B which still possess the general physical characteristics of lipids. Among these are included (1) saturated and unsaturated fatty acids, (2) mono and diglycerides and (3) alcohols. The alcohols are (a) straight chain water insoluble substances of higher molecular weight (from hydrolysis of waxes), (b) sterols and (c) alcohols containing the β ionone ring.

(D) *A miscellaneous group of lipids* which includes (1) aliphatic hydrocar-

bons, (2) carotinoids, (3) vitamins (A, E and K).

FATTY ACIDS

The simplest member of the series of saturated monocarboxylic acids is *formic acid*, the next *acetic*, the next *propionic*, the next *butyric*, and so on up the series. Fatty acids are straight chained even numbered mono carboxylic acids ranging in chain length from 4 to 24 carbon atoms. They are found in natural triglycerides. The acids may be either saturated or unsaturated. *Palmitic acid* ($C_{16}H_{32}O_2$) contains 16 carbon atoms arranged in a straight chain with a carboxyl group on a terminal carbon. *Stearic acid*, the next higher homologue is a straight chain aliphatic acid containing 18 carbon atoms. Both stearic and palmitic acids are *saturated acids*. They are esterified with *glycerol*. *Glycerol palmitate* and *glycerol sterate* are important esters in neutral fats. Fatty acids may be *unsaturated* and contain anywhere from one to six, sometimes even more, double bonds. *Oleic acid* has one, *linoleic* two, and *linolenic* three, and so on. Oleic and stearic acid have the same carbon content but oleic one double bond. Unsaturated acids occur more frequently in oils than in solid fats. The glyceride of oleic acid is a common component of olive oil and cotton seed oil. Practically all fatty acids found in nature are composed of an *even number* of carbon atoms. Fatty acids may also contain *hydroxyl groups*, *cyclic structures*, or *branched chains*. In some cases more than one carboxyl group is found. Combinations are also found in which both unsaturated linkages and hydroxyl groups occur. Castor oil, for example, contains *ricinoleic* acid which is an unsaturated hydroxy acid.

PHYSICAL AND CHEMICAL PROPERTIES OF FATS

The physical properties of a fatty acid or of a fat vary with its molecular weight and with its degree of unsaturation. In general the chemical behavior of fatty acids may be divided into those which are referrable to the carboxyl group and those due to the hydrocarbon chain. The carboxyl group confers water solubility. It is responsible for the ability to form salts (soaps) with metals such as sodium and potassium and esters with alcohols. The hydrocarbon portion causes the diminution of water solubility and is associated with oxidation and hydrogenation reactions. The carboxyl group is hydrophilic and polar, while the hydrocarbon is lipophilic and nonpolar. On water, a mono molecular layer forms with the carboxyl group oriented into water and the hydrocarbon group upright and parallel and oriented perpendicular to the water surface. Hydroxylation of a fatty acid increases its water solubility. Fatty acids may also be decarboxylated to form hydrocarbons. Some of these are known as caretenoids. The melting points of fats are not sharp since they are a mixture of several glycerides. The solidification temperature is lower than the melting point. Water solubility, generally speaking, is poor and volatility of compounds of high carbon content is low. Acids containing four or less carbon atoms are miscible with water; those that contain more are not. Volatility and water solubility decrease as molecular weigh increases. Volatility increases as the degree of unsaturation increases.

The *specific gravity* of lipids is less than that of water (0.913 to 0.914). Consequently they float on water. Unsaturated acids are more reactive than saturated due to the presence of the double

bonds. A molecule of water, hydrogen, oxygen or halogen may add at each double bond. Hydrogen passed through oils rich in unsaturated fatty acids adds to the double bond and forms saturated compounds. The oil is converted to a solid fat. The reaction is catalyzed by finely-divided platinum or nickel.

The esters of fatty acids possess a low degree of volatility and are poorly soluble in water. Lipids are soluble in organic solvents, such as ether, benzine, chloroform, acetone, or carbon tetrachloride. Esters of glycerol and fatty acids are called *neutral fats* since they have no free carboxyl group and are, therefore, neutral to indicators. If they remain in contact with air for any period of time, they may become acid in reaction because they slowly hydrolyze and oxidize (*become rancid*). Fats may be identified by determining their *melting* or *boiling points*. The index of refraction is occasionally used as a means of identification of individual fatty acids or esters.

HYDROLYSIS OF FATS

Fats are hydrolyzed in the body by enzymes known as *lipases*. *In vitro*, alkalies (sodium or potassium hydroxides) *hydrolyze* (saponify) fats into *sodium salts of the fatty acids* and *glycerine*. These salts are known as *soaps*. Frequently, a residue remains, known as the *unsaponifiable fraction*. This consists of *hydrocarbons* and *sterols* and other *nonhydrolyzable substances*. The number of milligrams of potassium hydroxide necessary to neutralize the total fatty acid contained in one gram of lipoid is known as the *saponification number*. The saponification number is an index of the quantity (molecular weight) of fatty acids contained in a lipid. Unsaturated

acids are usually estimated by determining how much a halogen, usually iodine or bromine, adds to the double bond. The degree of unsaturation is expressed in terms of the *iodine number* which is the percentage of iodine by weight in milligrams absorbed by one gram of lipid. The iodine and lipid are dissolved in carbon tetrachloride since they are mutually miscible in this solvent to facilitate the reaction.

STEROLS

Sterols are high molecular weight heterocylic alcohols. Cholesterol, ergosterol, phytosterol and vitamin D are sterols which are related to each other. They are all derived from the cyclopentanophenanthrene ring. This ring is also found in the sex and adrenal hormones, the bile salts and other biological substances. The close relationship of sterols to *carcinogenic hydrocarbons, steroid hormones, cardiac glycosides* and *bile acids* is noteworthy. Sterols are not lipids in the true sense but, since they are associated with lipids and esterified with fatty acids, they are usually included in classifications of lipids. The unsaponifiable residue, which amounts to approximately 1% of the total weight of fat, is composed chiefly of sterols.

Cholesterol is a mono hydroxy unsaturated alcohol which exists in the blood and tissues in both a *free* and *esterified* form. The concentration of the esterified form in plasma varies; that of the free form remains more constant. All tissues contain minute amounts of cholesterol but the brain and adrenal glands are the most richly endowed. The liver contains 0.24%, the spleen 0.36%, the brain 1.8%, and the adrenals 7.3% of cholesterol by weight.

ORGANIC AND CELLULAR FAT

Lipids are essential and *indispensable constituents* of all cells and tissues. In addition they also serve as the *medium for storage of energy* in the organism. The lipid contained in cells is often referred to as the *constant lipid element*. The cellular concentration is remarkably constant and changes little regardless of the state of nutrition of the organism. Cellular lipids are composed largely of *esters of unsaturated fatty acids*. They contain large proportions of phospholipids. The lipid content varies from organ to organ. If adipose tissue is excluded, *brain* and *nerve tissues* are the richest in lipid tissue content. However, one must remember that protoplasm is mostly *water* and that the total lipid content of all types of tissues is relatively small. Even brain and nerve which are, relatively speaking, rich in lipids contain less than one-fifth of the total weight of fat. For example, the lipid content of liver and muscle varies between 7% and 8% of the total weight. Nerve and brain tissue, even though richer in fat content, contains only between 12% and 15% lipids by weight.

BODY FAT (ADIPOSE TISSUE)

The term "body fat" is used to designate lipid depots which are stored for future energy sources by the organism. The term *adipose tissue* is more precise. This is often called the *variable lipid element*. Stored fat is formed from absorbed fats, carbohydrate and protein. Fat is usually stored in three regions of the body: in the *subcutaneous connective tissues*; in connective tissue surrounding viscera, such as the heart, kidney, and omentum; and *between muscle fibers*. Adipose tissue is mostly simple lipid. It does, however, contain small amounts of sterols and phospholipids. Approximately 90% of adipose tissue is *lipid* substances; the remainder is water, connective tissue, minerals and other elements.

COMPOSITION OF NERVOUS TISSUE

Nerve tissue includes brain, spinal cord, peripheral nerves, ganglia and plexuses. Nerve tissue is rich in lipid and, since anesthetics are lipophilic, these drugs are readily taken up by this type of tissue. Their composition will be described in some detail. Approximately 2% of the total body weight is brain and nerve tissue. Over 90% of the nervous tissue of the body is in the brain. Nervous tissue, in spite of its high lipoid content, is mostly water. Nerve tissue is referred to as *grey* and *white*. Grey matter contains more water than white. Fetal brain tissue contains more water than adult. The water content of brain decreases with age. Grey matter of adult brain is approximately 70% to 80% water. The solid constituents of nervous tissue are proteins (50%), lipids, salts and other extractives. The chief *proteins* in nerve tissue are collagen and a nucleoprotein. Albumin and globulin are also present but less abundant. The nucleoprotein contains approximately ½% phosphorus. Keratin is of an albuminoid nature. Neurokeratin differs from the keratin found in epidermoid tissues *but is similar to the latter in regards to insolubility and resistance to peptic digestion*. It is the protein found in axones, neurofibrils and filaments of nerve cells. Grey matter contains more protein than white. Peripheral nerve tissue contains less water than brain (68%); approximately 85% is protein, and approximately 15% lipids. In comparison, muscle contains 17% to 19% proteins and approximately 7.5% lipids.

Lipids of nervous tissue are chiefly *phospholipids, aminolipids, sulpholipids,* and *cholesterol.* The phospholipids of brain and nerve are chiefly *cephalin* and *lecithin.* Brain lecithin yields oleic, stearic, and phosphoric acids and choline when hydrolyzed. The cephalin of brain is not a definite compound. More than one type of lecithin has been isolated. Two of the three hydroxyl groups of glycerol in lecithins may be esterified with different fatty acids. The third hydroxyl group is combined with choline and phosphoric acid in all types. Each molecule of lecithin contains one molecule of unsaturated and one molecule of saturated fatty acid. Folch has shown that *cephalin* contains the nitrogenous base *amino ethanol* in one type serum and *inositol* in another. Therefore three different types have been isolated.

Sphingomyelin is a phospholipid which contains one molecule of fatty acid, choline, and a base known as a *sphingosine.* The fatty acids contained in sphingomyelins are linolenic and hydroxystearic. *Glycolipids* contains a carbohydrate and nitrogen but no phosphorus. Cholesterol is found as the ester and in the free form in both brain and nerve tissues. It is estimated that 99%

of the cholesterol in brain tissue exists as the uncombined form. Fat itself is not among the constituents of brain tissue.

Embryonic brain tissue contains approximately 10% lipids. This is the same quantity as the liver. As the fetus approaches term the concentration increases while that of the brain remains constant. The turnover of lipids in brain is slow. Using radioactive tracers it has been shown that 20% of the fat is replaced in a week. In the liver the turnover may be 50% in one day.

BLOOD LIPIDS

Lipids are present both in the plasma and the erythrocytes of whole blood. Plasma cellular lipids are partitioned according to chemical types. *Neutral fats, fatty acids, phospholipids, cholesterol,* and *cholesterol esters* are the most prominent plasma lipids. Cholesterol is perhaps the most important of blood lipids. Total lipid content of plasma varies from 570 mgm. to 800 mgm. per 100 ml. of blood. Approximately 350 mgm. of this are fatty acids, 150 mgm. neutral fats, 200 mgm. phospholipids, 200 mgm. cholesterol ester, and from 40 mgm. to 50 mgm. uncombined or free cholesterol.

RELATIONSHIP OF ANESTHESIA TO LIPID TISSUES

ABSORPTIONS OF ANESTHETICS BY LIPOIDS

It has been mistakenly assumed that lipid-rich tissues absorb more of an anesthetic drug than lipid-poor tissues because most anesthetic drugs are lipophilic. This is not necessarily correct. No doubt, solubility in lipids plays a major role in absorption. Yet, more important is the perfusion of a tissue by the drug.

Concentrations of anesthetic drugs in body tissue have been analyzed by numerous workers. These data are difficult to interpret because uncontrollable variables complicate in vivo studies. The uptake depends primarily upon how well the tissues are perfused. This depends upon the mass of tissue which comes into contact with a given mass of blood and the quantity of drug contained in the

blood, the diffusibility of the drug through the cells and the rate of blood flow. These factors vary not only from organ to organ but also with different states of activity of a given organ. Some tissues have a more abundant blood supply than others. Brain, for instance, has a rich blood supply (54 ml. per 100 gm. per minute). The subcutaneous fat perireneal, omental and other fat depots have relatively speaking, a poor blood supply. An organ whose cells are lipid-poor but are endowed with an excellent blood supply may absorb a greater amount of lipophilic substances than one which is lipid-rich but has a poor blood supply. The uptake, of course, varies with the blood concentration. The diffusion gradient depends upon this factor. Since there may be moment to moment variations due to changes in circulatory rate, pulmonary ventilation, and variation in inhaled concentration, this becomes an uncontrollable variable. It is not necessarily true that even though the arterial and venous blood concentrations are equal, that an equilibrium has been established between the blood and cells since there may be variations in cellular permeability to anesthetic drugs. Certain drugs penetrate the blood-brain barrier with greater ease than others. Some workers doubt the existence of such a barrier and ascribe the ready penetration of anesthetics into the brain to high lipid solubility. Brodie, Mark and others have shown that the ultra short acting barbiturates penetrate into the brain more rapidly than the longer acting (Chap. 19). The lipid solubility of ultra short acting barbiturates has been well established. Pittinger and his associates using radioactive xenon and tagged chloroform have indicated that

the uptake by the brain occurs at the same rate for both drugs and postulate that the blood flow through the brain is the determining factor as far as the brain is concerned. The lag in induction time which is noted with chloroform over xenon occurs in the lung and is due to the differences in rate of uptake of the two drugs at the alveolar membrane capillary interphase.

UPTAKE BY BRAIN AND ADIPOSE TISSUE

Interest in uptake of anesthetics by adipose tissues has been revived since the discovery, by Brodie and his co-workers, that ultra short acting barbiturates accumulate in adipose tissues. The thiopental content of the adipose tissues in the area of the kidney, omentum and subcutaneous tissue may be as much as fifty times as great than it is in muscle. Initially the barbiturate is distributed quickly and uniformly into the watery non-nervous tissues. Equilibrium is established within several minutes in all tissues except muscle and fat. Later the muscle (¾ hour) and the fat (1–2½ hours) reach a peak level; then they slowly desaturate. Data from excised adipose tissue during ether anesthesia show less drug in adipose tissue than brain. This is due to relatively poor perfusion of adipose tissue compared to brain. The release is correspondingly slow. Similar findings have been reported for cyclopropane. The bulk of cyclopropane is eliminated from the blood within ten minutes. Robbins detected traces in blood for several hours after conclusion of anesthesia. This apparently comes from the drug which passes into adipose tissue during induction and maintenance of anesthesia and which is released when the plasma is cleared. The clearance oc-

curs at a slow rate due to the fact that this tissue is not abundantly perfused.

Little if any correlation may be made between the fat content of tissues and the Overton-Meyer theory because of the forementioned factors. One must also remember that the Overton-Meyer theory applies to inert substances and excludes reactive materials. Local anesthetics, the barbiturates and numerous other non-volatile central depressants in many cases, have an anesthesiophore grouping in the molecule which is reactive (Chap. 20) and hydrophilic, as well as a lipophilic grouping. Local anesthetics, for example (Chap. 21) have a grouping which is oriented into the lipid phase of the lipo-metallo hydrophilic system of a nerve fiber. Local anesthetics are not inert. The basic form is lipid soluble.

UPTAKE BY NERVOUS TISSUE

The variations in solubility of a particular drug in different types of lipids contained in the tissues may also be responsible in the diversity of data available on this subject. Localization of anesthetics in greater concentration in one part of the brain than another has been postulated by some workers. However, this does not appear to be the case from the data on hand. Recent data using more refined techniques than those of earlier workers show that xenon, chloroform and various barbiturates are distributed in a nearly uniform manner throughout brain. One overlooked fact in considering lipophilic substances is that most tissues, including nervous, are chiefly water and the lipid content is only a fraction of the total solids.

Gensler, Nicloux, Hansen, and others analyzed tissues of animals anesthetized with ether, chloroform and various alcohols. They found that the brain absorbed more than other organs but the difference was not as remarkable. Organs having a profuse blood supply, such as liver, heart, spleen, kidney, and brain contain approximately the same amount of drug per unit weight of tissue. Apparently the distribution in tissues is a flow limited process which is not significantly influenced by differences in diffusion, permeability or chemical bonding. The differences in recovery time between volatile anesthetics are presumably dependent upon rates of transference at the blood-air interphase of the pulmonary bed and not due to differences in rates of transference or partitioning between the brain and blood. Analysis of subcutaneous, mesenteric, peritoneal and nerve (peripheral) lipid shows the concentrations of anesthetic drugs, such as ether and chloroform, are above those of other tissues. In some cases the concentration is ten times as much. The distribution in these tissues is proportional to the calculated amount which would be present if saturation were complete. Even so, the concentration is below the *calculated amount. This is explainable* possibly by the poor blood supply of these tissues. In these studies, the concentration in blood was usually above that of tissues.

PARTITION BETWEEN BLOOD
AND PLASMA

The partition of anesthetic drugs between plasma and corpuscles during surgical anesthesia varies with the type drug. Lipophilic anesthetics become concentrated in the cells. The hydrophilic drugs are found in greater quantities in plasma. Red cells contain less

drug than plasma. Four times as much *ethylene* is present in erythrocytes than in plasma. Concentrations of chloroform, cyclopropane and halothane in cells follow the same trend as ethylene. The higher content in red cells is attributed to uptake of the drug by the lipid of the cell. However, few studies are correlated with lipid content of both the plasma and cells. Plasma contains considerable lipid also, perhaps even more than red cells in some instances. Therefore, this stand cannot be justified. Plasma, as well as red cells, contains a large amount of cholesterol which may contribute to further variations in results obtained.

In summary, it may be said that brain, which is rich in lipid and has a profuse blood supply (55 ml. per 100 gm. of tissue per minute), but is still chiefly water, quickly absorbs more lipid-soluble anesthetic drugs than other tissues. The adipose tissues which are rich in lipids saturate slowly but once saturated may exceed all other tissues in uptake. Desaturation with adipose tissue is slow; that of brain comparatively faster.

CHANGES IN BLOOD LIPIDS DUE TO ANESTHESIA

The fact that blood lipids are influenced by anesthetics was suggested by Bibra, Harless and others who noted a relationship between the lipophilic quality of anesthetics and the lipid nature of nervous tissues. The effect of anesthesia upon blood lipids has been investigated by numerous workers since their time. Much of the data are not in agreement. This is probably due to variation in technique of analysis, depth of anesthesia, species differences, failure to partition the fractions of lipids, and failure to differentiate between serum lipids and cellular lipids. Boyd studied the effect of anesthesia on blood lipids in operated man following nitrous oxide-ether anesthesia. Morphine-atropine premedication was administered approximately one hour previous to induction of anesthesia. A differential analysis after anesthesia indicated a lowering of the neutral and phospholipid content of the red cell and plasma neutral fat. Twenty-four hours later a lipemia developed. The differential analysis indicated an increase in neutral fat, phospholipid, and cholesterol ester content of red cells, and a slight decrease in cholesterol and phospholipids of plasma. The saturated fatty acid fraction in plasma increased during the immediate postanesthetic period while more unsaturated fatty acids appeared later when hyperlypemia was present. The neutral fat of the cells showed an increase in this unsaturated fatty acid fraction during anesthesia while no change occurred in plasma. An increase of free cholesterol was observed during the interval of hypolipemia. Esterified cholesterol was unchanged. Other workers have reported changes in blood lipids using other anesthetics. Alcohol, ethylene, nitrous oxide, evipal, spinal and local anesthesia produce little change in blood lipid in man. Riecher, Bloor, Mann and others have noted that ether and chloroform raise the blood lipids in dogs. Free cholesterol is increased during ether and chloroform anesthesia. No significant change accompanies anesthesia with nitrous oxide, ethylene, or barbiturates. Increases in cholesterol during ether anesthesia may be related to disturbances in carbohydrate metabolism because the rise may be inhibited by previously administered insulin. The

significance of changes in blood lipids is difficult to evaluate. Whether or not they are due entirely to variations of cell volume per cent or to plasma volume changes is difficult to say. According to the state of our present knowledge of fat metabolism, these changes are of little clinical significance.

Starkenstien and Weden have noted a potentiation of the effects of chloroform, ether, barbital, and urethane narcosis following the intraperitoneal injection of cholesterol in experimental animals. Foldes and Beecher repeated these experiments and obtained similar results with ether and pentobarbital. Injection of olive oil potentiated ether narcosis but not that of pentobarbital. The exact significance of these findings is difficult to explain.

LIPID METABOLISM

The liver plays the dominant role in lipid metabolism. The liver contains a variable but significant proportion of lipids under normal conditions. After a fatty meal, the lipid content of the liver increases. In abnormal conditions and diseased states more abnormal fat than normal accumulates. The lipids of liver contain a higher proportion of unsaturated fatty acid, chiefly in the form of phospholipids and glycerides than do other tissues. Four phases of fat metabolism are ascribed to the liver: (1) Oxidation. (2) Desaturation of partly saturated lipid. (3) Synthesis from non-lipid substances. (4) Storage. The role of anesthesia in fat metabolism is not known.

Lipids are oxidized by a process known as β oxidation in which the β carbon of the fatty acid is attacked by oxygen. Each successive carbon is attacked in this manner until the entire molecule of acid is reduced to carbon dioxide and water. Glucose and insulin were once

believed essential for the complete oxidation of fatty acids beyond the 3 carbon stage. Recently, newer ideas have been evolved concerning the metabolism of fats. The older concept of β oxidation has been discarded and the idea that the entire fatty acid molecule is metabolized at one time by simultaneous oxidation at alternate carbon atoms with the subsequent formation of ketone bodies is now accepted. Also, the idea that insulin is essential to oxidize ketone bodies by coupling with carbohydrate has been revived. Ketone bodies can be utilized by cells for energy in the absence of carbohydrate. It is now believed that lipids are oxidized to ketone bodies in large amounts, when carbohydrate is not available, to provide the energy which normally is supplied by the carbohydrate. Ketone bodies can be utilized in the absence of carbohydrate. These end products *(ketone bodies)* accumulate in the blood. Two of these ketone bodies, hydroxybutyric acid and acetoacetic acid, are non-volatile acids. They combine with blood base and cause its depletion thereby contributing to a metabolic acidosis. Decarboxylation of the acetoacetic acid forms acetone which is a volatile ketone and not an acid. It is excreted by the lungs. Ketone bodies, although most commonly found in diabetes mellitus, may be noted in starvation, dehydration, and other metabolic disturbances. Only even-numbered fatty acids are subject to β oxidation.

The lipid present in the liver at any given time is a balance of the sum total of a number of factors: (a) the rate at which the blood supplies lipids to the liver; (b) the ability of the liver to absorb lipids; (c) the ability of the liver to oxidize, desaturate, or alter the lipids; and (d) the rate of synthesis of fat from non-lipid substances.

KETONE FORMATION DURING ANESTHESIA

Fats are hydrolyzed by enzymes and absorbed by the intestine aided by bile and bile salts. They pass into the blood; the greater portion passes via the lymphatics. No fat or phospholipids are eliminated in urine or sweat. Lipids are apparently eliminated by the gastrointestinal tract since feces contain from 6 to 12% lipid substances. This is usually of a different nature from fats found in food.

Ketone bodies increase in blood during anesthesia with most agents but particularly with ether, chloroform, and vinyl ether. This increase is most prominent if administration of anesthesia is continued for many hours. They form after the anesthesia has been in progress for a period of time but not early. The amount present contributes little if at all to the acidosis accompanying general anesthesia. Ketone bodies also form during the post-anesthetic period. The amount varies according to the previous state of nutrition of the organism and the degree of disturbance of other biochemical factors by anesthesia and operation.

The fat content of the liver has been noted to be increased following chloroform anesthesia in cases in which hepatitis developed. The chemical composition of the lipid in this condition is altered and differs in many respects from that encountered in that organ normally. Neutral fats increase; phosphatides decrease. The increase may possibly be due to inability of the liver to perform its function of desaturation and esterification of lipids. The deposits of lipid material appear in the center and midzonal areas of the lobules of the liver. The incidence of experimentally pro-

ated substances, such as carbon tetrachloride or chloroform is not increased if the liver is fatty. On the other hand, if fat is given orally several hours before the drug is administered, liver damage does result. The exact significance of this remains to be learned but it is additional evidence that the state of nutrition of the organism is an important factor in the development of liver damage.

There has been an attempt over the years to associate unexplainable phenomena during anesthesia with a lipemic state. It was postulated many years ago, without adequate evidence, that anesthetics dissolved lipids from the brain and transported them to the liver (Chap. 27). This fact was used in an attempt to explain narcosis. There is a periodic revival of this idea in an attempt to explain convulsions during ether anesthesia and to link this phenomenon with fat emboli. None of the evidence brought forth is convincing because it has been obtained in animals under conditions to which humans are seldom, if ever, exposed.

DEGENERATION OF NERVE FIBERS FOLLOWING INJECTION OF ALCOHOL

Histological changes are uncommon in nerve tissue after anesthesia. Blood borne (general) anesthetics and hypnotics cause no well-defined, clear cut specific changes in neurons. Local anesthetics may cause transient changes if the concentrations employed are excessive, but the clinically useful drugs if used judiciously are not locally toxic. The long-lasting drugs, however, do induce changes which may be categorized by the general term *neurolysis*. Such agents cause destruction of the axone at the site of application. When a nerve fiber is sectioned or the cell body of a nerve fiber

axone. They are characterized by chemical alterations of the contained lipids. The changes have been called *Wallerian degeneration*, named after Waller who first described them. The neurofibrils first become tortuous and irregularly thickened. The myelin becomes swollen and fragmented into ovoid segments and then undergoes chemical change. Droplets of lecithin and cephalin appear at first. Later glycerol-phosphates and unsaturated fatty acids appear. At this stage the fiber stains with metallo-organic compounds, such as silver, osmic acid and so on. The acids released from the lipid are apparently responsible for the staining properties. Subsequently, the cellular debris is cleared by phagocytosis. If the nerves possess a neurolemma, a hollow tube remains. If the cell body is intact the nerve regenerates by first sending in new neurofibrils into this tube and later redepositing the myelin. The process of regeneration requires months.

Direct application of caustic and dehydrating agents to nerve tissue results in destruction of the tissue. This is followed by Wallerian degeneration in the same manner as if the nerve had been sectioned surgically. Alcohol and phenol are employed for therapeutic nerve blocking to produce chemical sectioning. This is followed by death of the nerve. The degeneration which follows and the reaction observed in histological studies is Wallerian degeneration and differs in no way from that observed in surgical sectioning.

Application of 85% to 95% ethyl alcohol causes degeneration of both the sensory and the motor fibers of a peripheral nerve. Alcohol destroys mostly sensory fibers without affecting motor fibers when concentrations of approximately 30% or less are used. The selective action is an apparent one and is due primarily to differences in fiber size. The alcohol penetrates the larger fibers more slowly and with greater difficulty. However, it is capable of destroying all fibers whether motor or sensory, if these are small.

A latent period follows the injection of alcohol and similar caustic agents during which no apparent anesthetic effect seems to have developed. The delay is due to time required for the penetration of the drug into the nerve and for the degenerating action to begin. Anesthesia may be partial at first because small fibers are affected first. Later the effects of destruction of larger fibers become apparent. Injections of 5 ml. of 95% ethyl alcohol into experimental animals produce a zone of necrosis approximately 2 cms. in diameter. A few drops placed directly on a nerve are more effective and less destructive than a larger quantity injected perineurally. Changes caused by quinine and urea, solutions of procaine base in propylene glycol or oils, solutions of butyl para-aminobenzoate ester (butesin) in glycol and suspensions of procaine base are all due to neurolysis which produces histological changes similar to Wallerian degeneration.

Enzymes, Hormones and Vitamins

ENZYMES

ENZYMOLOGY

IN THE PREVIOUS CHAPTERS many instances have been cited in which the pharmacologic response of a drug was interrelated with some chemical reaction catalyzed by enzymes. Not only has enzymology become a highly specialized field of biochemistry but it also has assumed a high degree of importance in pharmacology. The list of enzymes is formidable and is rapidly growing. Techniques have been devised for their isolation from tissue slices, homogenates (purees) and even from preparations which contain intracellular bodies, such as nuclei, mitochondria, microsomes and so on.

CLASSIFICATION OF ENZYMES

Enzymes are "organic catalysts" elaborated by living cells. They are, however, capable of acting independently of cells. They do not initiate a chemical reaction but merely alter its speed. They do not themselves appear to have undergone any chemical change after the reaction is completed. As a rule they possess specificity. By this is meant that they catalyze only a particular type of reaction. The substance whose transformation the enzyme catalyzes is known as the *substrate*. The suffix "ase" usually indicates that a substance is an enzyme.

It is customary to name enzymes according to the type of reaction they catalyze. Thus, if an enzyme catalyzes a reaction of a hydrolytic nature it is called a *hydrolase*. If an enzyme is specific for hydrolysis of an ester it is called an *esterase*. If it hydrolyzes a protein it is called a *protease*. If it aids in the transfer of oxygen it is called an *oxidase*. If it catalyzes a reaction in which hydrogen is removed from a substance (dehydrogenation) it is called a *dehydrase*. If it aids in the removal of amino groups, it is known as a *deaminase*. Those endowed with specific functions are named according to this function. Thus, *urease* hydrolyzes urea to ammonia and carbonic acid and, therefore, is named urease after this specific reaction.

REACTIVITY OF ENZYMES

An enzyme is only detectable when it is combined with something upon which it acts. In other words, a substrate must be present to detect that activity. It is characterized as being "active" when the products of the reaction can be identified and measured. Enzymes are usually associated with other substances. A few enzymes have been obtained in a pure crystalline form by a continual fractionation. It must be remembered, however, that in a cell a particular en-

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zyme does not act individually. Instead, it may implement or may oppose the action of other enzymes. The activity of a cell is believed to be maintained by a mutual simultaneous integration of enzyme activity. The isolation of an enzyme as an individual chemical complex removes it from its natural habitat in which it is present in the cell and gives a distorted picture of its activity. The chemical reaction which an enzyme facilitates is known and generally fairly well understood. The interrelationship of this reaction with other reactions going on in the cell is not as clear. The quantitative significance of the reaction in the life of a particular cell or of the organism as a whole, likewise, is not clear.

NATURE OF ENZYMES

Each enzyme, irrespective of the type, contains a protein known as an *apoenzyme*. No enzymatic activity occurs without this protein. Many enzymes act only in the presence of another substance which carries a particular configuration referred to as the *prosthetic group*. This may be a coenzyme or a metal. Coenzymes are usually complex molecules which can be separated from the enzyme protein by dialyzing. Coenzymes are either organic or inorganic substances. They may be complex substances composed of several organic compounds as, for example, coenzyme I and II. Coenzymes may be ionic in character. For example, calcium ion which is essential for the conversion of caseinogen to casein by renin may be classed as one. Certain enzymes are elaborated in inactive forms known as proenzymes. These require activators to convert them to their active form. The activators are known as *kinases*. Pepsin is elaborated

as pepsinogen which is inactive but is activated by a substance, enterokinase, which converts it to pepsin. Coenzymes are required for completion of the reaction by certain enzymes involved in oxidative processes, such as dehydrogenases, flavoproteins and so on as well as by transferring, isomerizing enzymes. The metal ions often act as activators. The most important are calcium, magnesium, cobalt, zinc and manganese. They, too, are dializable.

MODE OF ACTION OF ENZYMES

How an enzyme facilitates a chemical reaction is not clear. It is believed that they first form intermediate compounds with a substrate by uniting with certain side chains known as prosthetic groups. These combinations of enzyme and substrate are unstable and break down to reform the enzyme and a new derivative. The substrate is transformed to new compounds in the breakdown but the enzyme reforms and appears not to be altered. Enzymes require proper environmental conditions for optimum activity. Each enzyme acts best at a certain optimum temperature, pH and concentration.

Certain tissues contain substances known as *antienzymes* which inhibit the action of enzymes. The pancreas elaborates a substance which combines with trypsin to inhibit its proteolytic action. An enzyme may either break down or synthesize a chemical substance, depending upon the environmental conditions and concentrations. Phosphatase, for example, may hydrolize phosphoric acid esters into an alcohol and the acid. On the other hand, if conditions of equilibrium and concentration are changed, it may favor the synthesis of the esters from the acid and alcohol. The function

of an enzyme is merely to accelerate a chemical reaction in the direction in which it is progressing. One striking feature of enzymes is that a relatively small amount catalyzes the changes of a large quantity of substastate.

DRUGS AND ENZYMES

Drugs, as has already been mentioned, may influence the activity of enzymes. For this reason they are of interest to anesthesiologists. Narcosis is believed by some to be due to inhibition of enzyme activity. This is described in more detail in Chapter 24. The development of the concept of competitive inhibition in drug activity has focused attention to the effect of drugs on enzyme activity. It is well known that many enzymes are inactivated irreversibly by drugs. Thus, these drugs are said to act as poisons. They may do so in a number of ways: (1) The drug may form a stable complex with the material with which the enzyme should act (substrate) and, thus, demobilize the enzyme. (2) The drug may combine with the active groups of the enzyme protein rendering the enzyme inaccessible to the substrate. (3) The drug may unite with the portion of the protein which is inert as far as the enzyme activity is concerned. This combination forms a new derivative and thus changes the properties of the protein as a whole. (4) The drug may combine with the coenzyme factor. This union may be with a prosthetic group or with a metal essential to initiate enzyme activity. (5) The drug may combine with the complexes formed between enzymes and substrates thereby preventing the new complex from dissociating and renewing the enzyme and releasing the product of enzyme action. (6) The drug may denature the enzyme protein. Usually this is irreversible.

Considerable attention is now being directed toward studying the action of drugs on the activities of enzymes. An attempt is now being made to explain drug actions on a chemical or physical basis at the molecular level. The quantitative determination of the amounts of drugs reacting with the active molecular groups in the cells may shed light on the kinetics of drug action. The recent developments in biochemistry have added much to our knowledge of the roles of specific enzymes in the chemical reactions of the cell. This has led to the study of the effects of drugs at receptor sites at cell surfaces. The discovery and utilization of the principle of competitive inhibition is an example. It is used extensively in the search for data on the mechanism of action of drugs.

Inasmuch as enzyme activity and drug action is a multi-varied study nothing more concerning this subject than the generalization which has been made is possible here. Specific details concerning individual situations are mentioned in the foregoing chapters in the general discussion of drugs.

HORMONES

INTRODUCTION

Hormones are often referred to as *chemical messengers.* Hormones are elaborated by ductless glands. Because of this they are often called internal secretions in contradistinction to secretions elaborated by the *exocrine glands* which have ducts. A *hormone* may be defined as a chemical substance elaborated by glandular structure in one part

of the body, which when carried by the blood to another organ or tissue, influences the physiological activity of that organ. Hormones, therefore, play an important role in chemical processes of the body. Considerable evidence has been presented which indicates that hormones are linked with enzyme activity in some way or other. Hormones exhibit considerable diversity of chemical structure depending upon the gland from which they are derived. A striking characteristic of hormones is that they are extremely active in small quantities. They exist in blood and in the glands which elaborate them in very minute quantities. A given hormone is chemically the same regardless of its plant or animal source. Thyroxin from human thyroid gland is identical chemically to that obtained from dogs, sheep or other animals.

An endocrine gland may secrete more than one hormone. The activities of most endocrines are interrelated. The hormone from one gland may influence the production of hormones in another. The pituitary appears to be the master or controlling gland. It exercises restraining or stimulating influences on most of the other endocrine glands by means of the multitude of hormones it elaborates.

Under certain conditions of diseased or altered physiologic states, a gland may be hypoactive and cause symptoms due to the reduction in the output of a hormone. In conditions where the glandular tissue proliferates, an excess of a hormone may be elaborated or an abnormal hormone may appear. Such glands are hyperactive. They then, give rise to syndromes characteristic of an excess of a given hormone or of liberation of abnormal quantities or of abnormal forms.

ANTI-HORMONES

Certain substances known as anti-hormones are present in tissues which counteract the effect of hormones.

Hormones of the Pituitary Gland

HORMONES OF THE ANTERIOR LOBE

The pituitary gland is divided into three portions, an anterior, a posterior and an intermediate part, each of which has a different anatomical origin. Because of the sharp physiological differences between the hormones derived in each of these lobes, they are usually considered separately. The quantities of pituitary hormones elaborated are so minute that they must be assayed by specific therapeutic responses in hypophysectomized animals. The important hormones elaborated by the anterior lobe are the (1) adrenotropic, (2) lactogenic,

(3) growth, (4) luteinizing, (5) follicle-stimulating and (6) thyrotropic. Extracts of the anterior lobe manifest specific hormonal effects. However, these effects cannot be linked to isolated, purified chemical substances according to our present knowledge. The hormones which have been isolated in the pure forms appear to be pure proteins. The thyrotropic hormone is the only one which has been obtained in a highly purified state but which does not appear to be a pure protein. The two hormones of greatest interest from the standpoint of anesthesia are the adrenocorticotropic and the thyrotropic. These are discussed further on.

ADRENOCORTICOTROPIC HORMONE

The adrenocorticotropic hormone has a specific stimulating action on the adrenal cortex. This hormone is also referred to as the adrenotropic hormone or ACTH. Hypertrophy of both the cortex and medulla have been observed in clinical syndromes characterized by an excess of this hormone. On the other hand pituitary cachexia is associated with atrophy of the adrenal cortex. The injection of adrenocorticotropic hormone in large doses into hypophysectomized animals causes hypertrophy of the adrenal cortex.

EFFECTS OF ANESTHESIA AND STRESS

It is possible that most forms of stress, including anesthesia, cause a general increase in sympathetic activity with the subsequent release of epinephrine and norepinephrine into the blood. This in turn causes an increased production of the adrenocorticotropic hormone (ACTH) by the anterior pituitary gland. This hormone then stimulates the adrenal gland to secrete more of the adrenocorticosteroid hormones. The ACTH release by the glands may also be controlled by the blood level of the adrenocortical hormones before the stress. If this is high, as it might be in patients who have been under treatment with the corticosteroids before coming to operation, adrenocortical function may be depressed. There may be, under these circumstances, a failure to respond normally to stress stimuli. A shock-like syndrome may develop which fails to respond to conventional forms of treatment. The phenothiazines (chlorpromazine) suppress the release of adrenocorticotropic hormones.

HORMONES OF THE POSTERIOR LOBE

The posterior lobe of the pituitary elaborates several hormones. The extract of the posterior lobe, pituitrin, yields two fractions, one of which contains pitressin and the other pitocin. Pitressin exerts a stimulating action on smooth muscle throughout the body. Thus, it may cause a pressor effect. Pituitrin is antagonistic to the action of insulin and if given in adequate doses is capable of preventing insulin shock. Pituitrin also increases the amount of fat in the liver, an effect which comes on rapidly but is of short duration. Protein metabolism is probably not influenced by the posterior lobe. Pituitrin also exerts a marked antidiuretic action. This is due to the pitressin fraction and comes about through the increased tubular absorption of water. Pitocin exerts an oxytoxic (contractile) effect on the pregnant uterus. Its action on other smooth muscle in other organs is negligible.

ANTIDIURETIC HORMONE

The form in which the antidiuretic hormone is stored in the gland is not known exactly. Extracts of the posterior pituitary containing the stored hormone yield a pure protein substance containing both the antidiuretic and the oxytoxic fractions. The oxytoxic and the antidiuretic principles are separated easily from the protein to which they seem to be bound. They have been isolated in pure form and found to be peptides. The pitressin fraction is now available in its synthetic form as vasopressin; the pitocin as oxytocin. Each of these peptides is composed of 8 amino acids, 6 of which are common to both. Those common to both are tyrosine, cystine,

aspartic acid, glutamic acid, glycine and proline. The two amino acids found in oxytocin not present in vasopressin are leucine and isoleucine; the two not found in the antidiuretic hormone are arginine and phenylalanine. Oxytocin and vasopressin each contain 3 amide groups. They are often described as being octapeptide amides.

ANTIDIURESIS AND ANESTHESIA

The antidiuretic hormone and vasopressin are now known to be one and the same thing. The antidiuretic hormone increases the rate of reabsorption of water from urine in the renal tubules without modifying the rate of glomerular filtration. The hormone presumably does not alter reabsorption of water by the cells of the proximal convoluted tubules. During anesthesia an increased liberation of antidiuretic hormone occurs with a subsequent reduction in urinary output. The urinary excretion of the hormone is increased. The relationship of this hormone and urine formation is also discussed in Chapter 33.

HORMONE OF THE INTERMEDIATE LOBE

The intermediate lobe secretes intermedin whose function is to increase the deposition of melanin by melanoblasts of the skin. Hydrocortisone and cortisone both reduce the activity of this hormone. No relationship between anesthesia and this hormone is known.

Hormones of the Adrenal Gland

STRUCTURE OF THE GLAND

The adrenal gland is divided both anatomically and functionally into two portions, an outer cortex and an inner medulla. The cortex is composed of a narrow rim of cells surrounding the adrenal medulla. Both portions secrete important hormones. The medullary hormones, epinephrine and norepinephrine, are of considerable interest in both physiology and pharmacology and are of extreme importance from the standpoint of anesthesia. These substances have been described in conjunction with the autonomic drugs in Chapter 15.

The cortical area is delineated into three zones, a glomerular, fascicular, and reticular. The characteristics and arrangement of the cells differ in the three zones. The zone nearest the capsule (glomerular) contains cells which are more or less arranged in loops. The middle zone (fascicular) contains cells which are arranged in parallel strands.

The most centrally located zone is referred to as the reticular zone. All three layers produce a group of hormones referred to as the steroid hormones (or corticosteroids, corticoids).

STEROID HORMONES

The adrenal cortex is essential for life because it secretes the vital steroid hormones. Approximately 30 steroid hormones have been isolated from the cortex. Of these a half dozen are physiologically important. The human adrenal cortex secretes primarily hydrocortisone, aldosterone, corticosterone, and androstenedione. Cortisone and desoxycorticosterone are biologically potent steriods but they apear to be unimportant, natural secretory products of the adrenal gland. Many of the numerous hormones which have been isolated are of little practical interest. It has been suggested that they are artefacts which develop during the tedious manipulations in the

study of the chemistry of adrenal physiology.

CHEMISTRY AND CLASSIFICATION

The important adrenal corticosteroids may, from a chemical standpoint, be placed into two groups. All are derivatives of the hydrocarbon nucleus called the cyclopentanophenanthrene ring. Each has 21 carbon atoms (Table I.35). Carbon 20 and 21 appear in the form of a keto chain attached to position 17 on the pentane ring. In the first group are derivatives which have a hydroxyl radical at the 17 position. They are called collectively the 17 hydroxy corticosteroids. In the second group the hydroxyl at position 17 is absent. Therefore, they *are called 17 desoxycorticosteroids. The term desoxy refers to the fact that once upon a time an oxygen was present on a structure but that it has been removed. This must be distinguished from the term dehydro which indicates that hydrogen atoms have been removed from a particular position. Each of these two groups is composed of at least three specific compounds. Each differs from the other only in the fact that the* 11 position is occupied

TABLE II.35

Positions			Com-	Name
17	11	3	pound	
—OH	=O	=O	E	Cortisone
—OH	—OH	=O	F	Hydrocortisone
—OH	H	=O	S	Desoxyhydroxycorticosterone
—H	=O	=O	A	Dehydrocorticosterone
—H	—OH	=O	B	Corticosterone
—H	H	=O	D	Desoxycorticosteroid

by (a) a ketonic group, (b) a hydroxyl group or (c) a hydrogen atom (desoxy group) (Table II.35). The 17 hydroxy compound having a ketone on position 11 was called compound E (cortisone) by Kendall; the one having the hydroxyl on position 11 was called compound F (hydrocortisone). Cortisone and hydrocortisone were among the easiest of these hormones *to synthesize and, thus, became available for clinical use long before the others. All compounds in both groups have a keto group in position 3.*

Other substances besides the characteristic adrenal corticosteroids are present in the adrenal cortex. Some of these resemble the estrogens and progesterones, while others are similar to the androgens. A large quantity of ascorbic acid is also found in the adrenal gland.

TABLE I.35
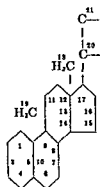
Cyclopentanophenanthrene Ring and Added Carbon Chains   17-Hydroxycorticosteroids   17-Desoxycorticosteroids
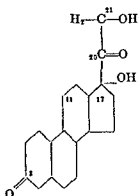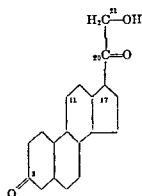
An interrelationship exists between ascorbic acid and certain of the adrenal steroids but to date there is no conclusive evidence that indicates what its role in adrenal physiology may be.

Group I, which includes the 17 hydroxy corticosteroids, is composed of cortisone, hydrocortisone, 11-desoxy 17-hydroxy corticosterone and pregnisolone. These fractions manifest anti-inflammatory activity, such as is encountered in various forms of arthritis and associated collagen diseases. They favor the breakdown of tissue proteins to amino acids and the synthesis of glucose from these acids (gluconeogenesis). They cause a suppression of eosinophils and lymphocytes which causes them to disappear from the blood stream. Hydrocortisone is the chief fraction of this group in the human adrenal. It has a greater water solubility than the others and can be given intravenously.

Group II is composed of the 17 desoxy corticosteroids. This group includes dehydrocorticosterone, corticosterone, desoxycorticosteroid acetate (DOCA) and aldosterone. These fractions largely influence the selective retention of water and sodium and the selective excretion of potassium by the renal tubules. Aldosterone has a salt retaining activity 10 times that of desoxycorticosteroid. Aldosterone is a naturally occurring steroid which can be isolated from normal blood and urine. It differs chemically from desoxycorticosterone acetate in that it has an aldehyde group on position 18 instead of a methyl group. Androgen, estrogen and progesterone which are also present in the gland are responsible for secondary sex characteristics. One point needs emphasis. Overlapping of action occurs between the members of the three groups of hormones. The androgens pro-

duced by the adrenal cortex are also important in promoting tissue or protein anabolism. Loss of axillary hair in women with Addison's disease reflects diminished adrenal cortical production.

MAJOR TYPES

Three major types of hormones, then, may be ascribed as being present in the adrenal, those concerned largely with metabolism (glucogenic), those concerned with secondary sex characteristics (androgenic) and the mineral corticosteroids (sodium retaining). An excess of these three types produces well defined syndromes. An excess of the glucogenic hormone results in Cushing's syndrome. An excess of the androgenic hormone produces the adrenogenital syndrome. An excess of the mineral regulating type of steroids produces aldosteronism which is characterized by a loss of electrolytes and water. A deficiency of certain or all cortical hormones results in a syndrome often referred to as Addison's disease.

Besides the forementioned basic functions the adrenal cortical hormones (1) decrease membrane permeability, (2) decrease fibroblastic proliferation, (3) alter immune reactions, (4) decrease central nervous system excitability, and (5) cause regulation of melanin pigmentation.

RELATIONSHIP TO OTHER GLANDS

Important but complex relationships exist between the adrenal glands and other endocrine glands. The activities of the anterior pituitary, the adrenal cortex, the thyroid, the pancreas and the gonads are all interrelated. The pituitary is the master regulator of the hormonal system. The adrenal is one of its target glands. The anterior pituitary as has been mentioned previously secretes a

hormone known as the adrenocorticotropin (ACTH) which has a strong stimulatory effect on the elaboration of the adrenal cortical hormones. Excess activity of the pituitary stimulates the adrenal and causes it to hypertrophy. The rate of formation of ACTH by the pituitary varies with the stimuli from the hypothalmus and the level of circulating adrenal cortical steroids.

RESPONSE TO STRESS

The adrenal responds to stress by increased production of corticoids. Harmful exogenous stimuli, such as tissue damage, psychic stress, pronounced changes in environment and anesthesia were found by Selye, in 1947, to enhance the pituitary-adrenal response. This response is also known as the stress reaction or the "alarm" reaction. It is assumed that this response is beneficial because it enables the body to better resist the deleterious effects of injury. The pathway through which this stimulation of the adrenal comes about is via the pituitary. This gland liberates ACTH which in turn increases the output of adrenal corticosteroids. The steroids themselves provoke metabolic and other changes in the peripheral tissues similar to those observed following injury.

It is possible, then, for an acute adrenal cortical insufficiency to follow the sudden severe stress, particularly if the function of the gland is inadequate to cope with the stress. The clinical features of this entity evolve rapidly once precipitated. The symptoms include nausea, vomiting, profound weakness and circulatory collapse. Adrenal crises are especially common in Addison's disease after stress due to trauma, operation or anesthesia or an emotional storm. They may accompany other conditions, such

as overwhelming infections, pneumonia, typhoid fever or they occur in a person with a previously normal adrenal function who has developed a relative insufficiency of the pituitary-adrenal axis following discontinuance of ACTH, cortisone or other corticoid therapy for some disease, such as rheumatoid arthritis and allergic states or other diseases. These individuals tolerate stress poorly, as a rule. They should have additional steroid therapy when major surgery is contemplated.

Adrenal cortical insufficiency is characterized by dehydration and potassium ion retention since sodium ion is lost into the urine and water is lost with it. Patients receiving steroids retain sodium and lose potassium.

EFFECTS OF ANESTHESIA ON CORTICOIDS

An increase in the blood level of active adrenal cortical substances is noted during anesthesia. Ether anesthesia produces the greatest rise while thiopental, nitrous oxide and spinal anesthesia produce the least. The increased corticoid blood levels may be due to (1) increased production of these substances by the adrenal cortex, (2) to a decrease in liver function which might alter the rate of conjugation of these steroids and (3) to a decreased renal function which might prevent the excretion of corticoid substances. There is ample evidence to suggest that conjugation by the liver is not at fault and that increased blood levels are definitely due to adrenal cortical stimulation. Analysis of the venous blood from the adrenal gland in dogs during narcosis induced and maintained with different anesthetics reveals an increase. It is difficult to say why the response is different among different anesthetic

agents. The technique of administering ether anesthesia may be responsible for the increased level since induction is more difficult with this agent. The change during spinal anesthesia might be explained by the fact that the hypothalamus may be stimulated both neurogenically and by hormones as well. Therefore, even though the afferent impulses are blocked, stimulation of the adrenals may still proceed by hematogenous transport of hormones. Anesthesia, if it does play a role, appears to play little more than a minor one. Surgery is a far greater and a major stress.

HYPOTENSION AND ADRENAL HYPOACTIVITY

A normal patient reacts to stress by an initial increased adrenocortical activity. He survives the ordeal but a depression of activity may ensue later manifested by a hypotension and decreased steroid output. A patient may have a high plasma hydroxy corticosteroid level, yet the tissue receptivity may be so altered, for one reason or another, that the cells are not able to respond. The vascular system may not respond to pressor amines and an existing hypotension may not respond to blood transfusion and fluids because of this altered tissue response to the corticoid. The presence of a hypotension which does not respond to usual therapeutic measures during an operation, however, is not necessarily an indication of adrenocortical insufficiency. Other factors may operate. The positive inotropic action of catechol amines, for example, is absent in the presence of respiratory acidosis, whereas if alkalosis is present the response of the heart to the pressor substances is good. A mechanism appears

to be present which is responsible for an increase in circulating level of hydroxy corticosteroids. It could be due to some mechanism which delays the disappearance of these substances from the blood instead of one which causes an increased production. One other consideration is noteworthy. In shock, the circulation may be inadequate to perfuse the adrenal gland as well as the tissues to which cortical substances are delivered. Uptake is thereby impaired and the cells are inadequately supplied.

BLOOD LEVELS OF STEROIDS

A rise in circulating corticosteroids may indicate several processes. It may indicate an increased activity of the adrenal. On the other hand, it may be a manifestation of decreased hepatic destruction or conjugation of the hormone. It may also indicate decreased renal excretion due to altered tissue utilization. The urinary excretion of 17 hydroxy corticosterone does not reflect a true picture of the over-all adrenal cortical response to surgical trauma, since both the conjugated and active hormones are measured simultaneously by this test. More would be learned by studying circulating blood levels of active adrenal cortical hormones as they influence body tissues. The fact that the adrenal responds with increased production is not necessarily the important consideration. How the cells respond to the excess is more important. The greater the magnitude of the operation, the greater the cortical response. The influence of age has been incriminated in the adrenal response. It has been said that the older patient does not respond as well or with adequate levels as the younger. This has been found not to be so. The adrenal

cortical response in the aged appears to be equally as good as that of other age groups. The only reason for a possible decreased tolerance to stress in the aged is the diminished vascular reactivity which these subjects manifest.

Hormones of the Thyroid Gland

FUNCTION OF THE GLAND

The thyroid gland is essential for the control of metabolic activity. This activity is conferred by an iodine containing globulin known as thyroglobulin. Besides thyroglobulin two other iodine containing substances are found in the gland, *thyroxine* and *diiodotyrosine.* The latter compound is inactive physiologically. However, it acquires activity when it combines with a protein. Thyroxine is a crystalline, iodinated, amino acid. The physiological activity of thyroglobulin is greater than that of thyroxinin in its free form. Diiodotyrosine is considered to be the precursor of thyroxine. Radioactive iodine is rapidly incorporated into thyroglobulin. It makes its first appearance as diiodotyrosine. Anti-thyroid drugs, such as thiouracil, propylthiouracil, methylthiouracil and thiourea prevent the gland from incorporating inorganic iodine into the organ. Gradually, the active thyroid compounds are reduced. The thyroid hormone catalyzes oxidative processes in tissues. Thus, it elevates the general metabolic rate. Thyroxin influences carbohydrate metabolism and causes glycogenolysis.

ANESTHESIA AND THYROID FUNCTION

The effects of anesthesia upon the thyroid gland are not clearly understood. Little data is available particularly in man. If for no other reason the thyroid gland and its hormones are of interest in anesthesia because they influence the metabolic rate. Hyperactivity of the thyroid gland and hypersecretion and administration of endogenous thyroxin cause an increase in metabolic rate. Oxygen consumption, carbon dioxide excretion and heat output are all increased.

Kohn-Richards observed that preliminary administration of thyroxin to frogs *increased their susceptibility to sodium thiopental narcosis.* Similar responses have been reported for man during chloroform and ether anesthesia. The effect following ether was less pronounced *than with chloroform. Thyroxin has been* recommended as an antagonist for severe depressions due to hypnotic and narcotic overdosage, such as avertin, the barbiturates and morphine. The hormone is of questionable value for such purposes because a latent period of a number of hours must precede the onset of physiological action of the hormone. By the time the effect is established it may be too late.

Recent investigations suggest a possible relationship between surgical trauma and altered thyroid function. Some workers postulate that the thyroid gland is an important participant in the response to stress. Hayes and his associates noted an increased utilization of thyroxine in surgical patients. Their data suggests that the thyroid gland is activated by operation and that there is an increase in utilization of endogenous thyroid hormones. Thus, increased level of circulating hormone is present in the face of increased utilization.

The factors altered by anesthesia which might influence function of the thyroid secondarily are many. Variations in kidney function, blood circulation, degree of central nervous system stimulation, activity of the pituitary and the adrenals may upset thyroid function. Some investigators have suggested that thiobarbiturates directly depress the activity of the thyroid gland because they are closely allied to the antithyroid drugs. The antithyroid drugs are thioamides. The most prominent of these contain thiourea, which is also present in the thiobarbiturates. Thus, thiouracil, propylthiouracil and related compounds are allied to the thiobarbiturates. The mode of action of antithyroid drugs is not known with certainty. They appear to affect the iodination of tyrosine. They do not prevent the accumulation of iodine in the gland. It may be that they compete with the substrate for iodine. Thiourea which forms the basis of thiour-

acil and other antithyroid drugs is likewise present as the thiourea residue in thiopental. Thus, they inhibit the formation of thyroxin and thyroglobulin. They do not interfere with the action of injected thyroxin.

IODINE UPTAKE DURING ANESTHESIA

The effect of anesthesia on the uptake of radioactive iodine has been studied by Oyama. Cyclopropane and ether both inhibited the two hour thyroid uptake in rats. Ether likewise depressed the activity. A significant depressant effect was obtained when thiopental was used. With ether and cyclopropane the uptake was normal within 24 hours. This was not the case with thiopental, however. Little data of significance in humans is available. Free iodinated amino acids such as tri-iodothyronine may exert a role in thyroid function. Iodides administered during anesthesia are ineffective.

Hormones of the Parathyroid, Gonads and Other Glands

A discussion of the hormones derived from the male and female gonads in the body is a superfluous undertaking at this time and serves no purpose here, since no definite relationship has been established between their activity and clinical anesthesia.

PARATHYROID AND PARATHORMONE

Parathormone is a hormone elaborated by the parathyroid gland which controls calcium-phosphorus metabolism. No relationship has been established between parathyroid activity and anesthesia.

THYMUS

Little specific information is available

concerning the secretions of the thymus. The thymus was once incriminated in unexpected deaths occurring during anesthesia. No relationship has been established between the thymus gland or any secretion in the so-called status thymolymphaticus. Some inconclusive evidence has been presented suggesting a relationship between an enlarged thymus and adrenocortical hypofunction. This remains to be confirmed.

GASTROINTESTINAL HORMONES

No realtionship has been established between the hormones elaborated in the gastrointestinal tract, such as gastrin, secretin, cholecystokinin, and enterogasterone and anesthesia.

VITAMINS

GENERAL NATURE

Vitamins are essential exogenous substances obtained from food. Their chemistry has been little understood until recent years. Apparently they play diversified but important roles in cellular reactions. Considerable evidence exists that they are important in cellular oxidations. They are usually considered together in one group because they are associated with nutritional processes. Until recently vitamins were classed according to their solubility in water or lipoid and were identified by using letters of the alphabet. Recently, as more has been learned of their structures, physiological behavior and reactions, there has been a departure from this method of classification and they have been classed as are other biochemical substances—according to structure, function or source. Certain vitamins which were formerly believed to be single substances have been found to be complex mixtures. Notable among these is vitamin B, which has been referred to as the Vitamin B complex because it is composed of nearly a dozen dissimilar chemical substances. The exact relationship of vitamins to anesthesia and operation still remains to be determined. They should be of interest to the anesthetist because they are intimately concerned with enzymatic and other biochemical reactions going on within the organism. The identification and assay of vitamins has been difficult but has recently been simplified to a certain extent by the introduction of micro-techniques involving fluorometry. Heretofore tedious biological assays were necessary and data obtained were nowhere near as specific.

Vitamin A

CHEMISTRY

The term *vitamin A* has been used to designate a number of chemically and physiologically related substances. The sources of these vitamins are certain plant pigments known as carotenes or carotenoid pigments. Three carotenes, α, β, and γ carotene have been described which yield the vitamin. Beta carotene splits into two molecules of vitamin A. The α and γ carotenes yield only one molecule of the vitamin. Carotenes are all formed in plant life but after ingestion by animals are transformed to vitamin A by the liver (in man). Chemically, vitamin A is a high molecular weight alcohol. Two fractions have been described, A_1 and A_2. Vitamin A_2 is 1/100 as potent as A_1. Vitamin A is easily destroyed by oxidation and heat. It is stored in the liver (90% to 95%) in the form of esters.

FUNCTION

Vitamin A and related products are fat soluble substances. They are absorbed from the gastrointestinal tract as are fats. Bile is essential for their absorption. Vitamin A is essential for proper function and resistance of epithelial cells throughout the body. Atrophy of epithelial tissues and nyctalopia, or night blindness, results in cases of deficiency. The vitamin is essential for the synthesis of visual purple (Rhodopsin).

One might anticipate an association between this vitamin and anesthesia in view of the fact that both are lipoid soluble. No relationship has been found to exist, however, and it is doubtful that any exists.

Vitamin D

CHEMISTRY

The term *vitamin D* has been used to designate a group of related substances, all of which are sterols, and all of which are found in nature. These substances are essential for the absorption and metabolism of calcium and phosphorus. Two forms of the naturally occurring vitamin D are known. One of these is often referred to as *calciferol or viosterol* (vitamin D₄). This is obtained by the irradiation of ergosterol which is related to and almost similar in structure to cholesterol. Ergosterol is referred to as a provitamin D₂. It is found in ergot and yeast. If 7, dehydrocholesterol, a sterol found in the skin and milk, is irradiated, vitamin D₃ forms. This occurs in nature in fish liver oils. Vitamin D is absorbed after oral, subcutaneous, and intramuscular administration. Bile is essential for its absorption from the intestine. The exact fate of vitamin D in the body is not known. However, the vitamin is not destroyed by the tissues. Vitamin D is slowly excreted.

FUNCTION

Exactly how vitamin D increases the retention of calcium and phosphorus is not known. Some investigators feel that vitamin D aids in the absorption of calcium and phosphorus; others feel it acts locally to aid in the decomposition of calcium and phosphorus salts. The vitamin is essential for the prevention of rickets. There is no known relationship between the vitamin and anesthesia and it is doubtful that any exists.

Vitamin E

CHEMISTRY

The term vitamin E, as is the case with other vitamins, designates a group of compounds which possess vitamin E activity known as the tocopherols. Tocopherols are alcohols. Three alcohols are known which have the biological function of this vitamin—α, β, and λ tocopherol.

FUNCTION

Vitamin E is essential for sexual function of rats and other experimental animals. The exact role of the vitamin in the human is not known. However, it is believed that vitamin E is essential for the auto-oxidation of fats. The most striking property of the tocopherols is an anti-oxidant activity which appears to be directed principally to fats. Fat from vitamin E deficient animals is abnormally subject to oxidation. However, this may be stabilized by α tocopherol. The tocopherols protect vitamins (A) from oxidation if added to food. Recent studies show that the vitamin is of benefit in the treatment of muscular dystrophies in animals. However, this has not been found to be so in man. The exact relationship of the vitamin to human disease is not known. No relationship has been established between the vitamins and anesthesia and it is doubtful that any exists.

Vitamin K

FUNCTION

Vitamin K is of intense interest in surgery since it catalyzes the formation of prothrombin which is one of the necessary factors for clotting of blood. The formation of prothrombin is largely

dependent upon components of the hepatic parenchyma. Advanced hepatic damage may be accompanied by hypoprothrombinemia even though the supply of vitamin K is ample. Vitamin K deficiency causes uncontrollable hemorrhage. The vitamin is widely distributed in foods. The enzyme may also be synthesized by the organisms of the intestine. In the first days of life the intestinal flora may not produce enough vitamin K for the infant's needs. This may lead to hypoprothrombinemia. Vitamin K competes inhibitively with coumarin and drugs of its type and reverses their anticoagulating effect.

CHEMISTRY

Vitamin K is a *fat soluble* substance which is readily absorbed from the intestinal tract. The vitamin, which was discovered by Dam (1935), has been resolved into two naturally occurring substances whose basic configuration is naphthoquinone. These were called vitamins K_1 and K_2. Both have been synthesized. A number of other naphthoquinone derivatives have been prepared which possess the activity of the vitamin. A normal liver can produce prothrombin only if enough vitamin K is present. The diet must contain vitamin K or its precursors at all times since the vitamin is not easily stored in the body. As is the case with other fat soluble vitamins bile is essential for absorption of the vitamin. Prothrombin deficiency results if liver function is impaired, or bile is absent in the gastrointestinal tract. In obstructive jaundice the absorption of vitamin K may be poor and inadequate formation of prothrombin results.

Although no relationship has been established between vitamin K and anesthesia, its importance in surgery cannot be over-emphasized because of the role it plays in hemorrhagic states. Difficulties may arise due to deficiency.

Vitamin B Complex

The term *vitamin B* has been used to designate a group of important vitamins. The entire group is better known as the *vitamin B complex*. Most of the individual members in the vitamin B complex have been identified and synthesized. The complex is now known to include thiamine (B_1), riboflavin (B_2), niacin (P-P factor), pyridoxine (B_6), pantothenic acid, lipoic acid, biotin, folic acid group, inositol, para-aminobenzoic acid and vitamin B_{12}.

Thiamine

CHEMISTRY

Thiamine chloride was one of the first members of the complex to be studied. The substance is a complex base which forms salts with acids. It is available synthetically in the form of the hydrochloride. The hydrochloride is a white, water soluble powder which is stable and may be heated in acid solution without disturbing its potency. Most tissues, particularly the liver, brain, heart and kidney may store the vitamin. However, the capacity to do is limited. High vitamin diets favor storage of small quantities but the excess over basic requirements is eliminated in the urine. Vitamin B is inactivated in the body. The rate of destruction is accelerated when there is an increase in

metabolic rate, exercise, or ingestion of thyroid extract.

FUNCTION

Absence of the vitamin causes polyneuritis, gastrointestinal, and vascular disturbances, hypotension and failure of the right side of the heart. Endocrine disturbances also accompany extreme deficiency.

The vitamin forms a diphosphate (thiamine pyrophosphate) which acts as a *coenzyme* in carbohydrate metabolism. This coenzyme facilitates the decarboxylation (splitting off of carbon dioxide)

from keto acids of the type exemplified by pyruvic or alphaglutaric acid. Without it the organism cannot convert pyruvic acid to acetic aldehyde and carbon dioxide. The acid then accumulates in nerves and tissues.

No direct relationship of the vitamin to clinical anesthesia has been established. The vitamin however is concerned with carbohydrate and phosphoric acid metabolism. These metabolic processes are disturbed during anesthesia. Thiamine antagonizes to a certain extent the action of non-depolarizing drugs. (Chap. 23).

Riboflavin

CHEMISTRY

Riboflavin (also known as lactoflavin, vitamin B_2 and vitamin G), is one of a group of yellow fluorescent pigments known as *flavins*. Riboflavin is involved in intermediary metabolism. The substance is heat stable, water soluble, and may be crystallized in the form of yellow-orange needles. Riboflavin is distributed throughout all body tissues. The concentration in various organs remains fairly constant. The vitamin is essential *for growth, for function of the nervous* system, and for nutrition of the skin.

Cataracts, corneal opacities, and disturbances of the skin may result from a deficiency of the vitamin. Biochemically, the vitamin is important as a *coenzyme* in oxidative processes characterized by hydrogen transfer. In the cell it serves both as a *hydrogen donator and acceptor*. The enzymes are called flavoproteins. Two forms of riboflavin exist in enzyme systems, riboflavin phosphate (riboflavin mononucleotide) and flavin adenine dinucleotide (FAD) (Chap. 27). *There is no known relationship between* the enzyme and anesthesia.

Nicotinic Acid (Niacin)

CHEMISTRY

Nicotinic acid is also a member of the B complex. The structure is a 3-pyridine carboxylic acid. Nicotinic amide (Niacin amide) is also associated with nicotinic acid and is physiologically as active as nicotinic acid. Nicotinic acid is a water-soluble, white powder composed of needles which possess a slightly bitter taste. Solutions of nicotinic acid may be sterilized by heat.

FUNCTION

The vitamin is readily absorbed from the gastrointestinal tract and is excreted into the urine as a conjugate or as a methylated derivative. Nicotinic acid is biochemically important because it functions as a constituent of two important enzymes, diphosphopyridinenucleotide (DPN, coenzyme I) and triphosphopyridinenucleotide (TPN, coenzyme II). The function of both enzymes has been de-

scribed in Chapter 27. DPN is composed of two molecules of a pentose sugar, d₁ ribose, two molecules of phosphoric acid and a molecule of the purine base adenine. TPN differs from DPN only in the presence of one additional phosphoric acid esterified to the hydroxyl group of the second carbon of the ribose attached to the adenine. The two enzymes are inter-convertible. They both function as hydrogen carriers. Each becomes reduced by accepting an atom of hydrogen from the metabolite. One atom of hydrogen is transferred from the metabolite. A third pyridine nucleotide has been discovered which is called coenzyme III. The amino acid, tryptophan, normally contributes to the nicotinic acid supply of the body. Nicotinic acid is essential for the formation of glutathione and in sulphur metabolism. Deficiency of nicotinic acid results in pellagra.

Although the vitamin is related to the alkaloid, nicotine, their physiological functions do not in any way resemble each other. Nikethamide, a drug widely employed as an analeptic, is the diethylamide of nicotinic acid. This relationship in the light of present day knowledge is merely coincidental. Nicotinic acid is relatively non-toxic.

No definite relationship has been established between nicotinic acid and clinical anesthesia. However, the relationship of the enzyme to *respiratory enzymes* is of interest since enzyme activity is influenced by drugs. Narcotics may cause suppression of cellular oxidation, *even though it is now well established that the dehydrogenases are not included among those enzymes which may be suppressed during anesthesia* (Chap. 27).

Pantothenic Acid

CHEMISTRY AND FUNCTION

This vitamin is also one of the numerous members of the vitamin B complex. It occurs in large amounts in yeast, liver and wheat germ. The enzyme is extremely important in metabolism. The enzyme is important as a constituent of coenzyme A (acetylase). This coenzyme is essential for reactions involving acetylation. For example, it is utilized by combination with oxalacetic acid to form citric acid which initiates the tricarboxylic acid cycle. It is responsible for the combination of acetic acid with choline to form acetyl choline or with drugs such as sulfanilamide which are acetylated prior to excretion. Animals deficient in the enzyme exhibit hemorrhage and necrosis of the adrenal cortex and an increased appetite for salt. Acetic acid is a precursor of cholesterol and of the steroid hormones. The acetic acid used for this synthesis is catalyzed by coenzyme A. The enzyme is essential in the metabolism of carbohydrate, protein and fat. It has been synthesized.

Pyridoxine

CHEMISTRY

Pyridoxine is also a part of the vitamin B complex. Chemically it is related to nicotinic acid since it is a pyridine derivative. The vitamin was once referred to as vitamin B₆. It occurs in yeast, liver

and wheat germ. It was once known as the anti-dermatitis factor. Pyridoxine is not the most active form of the enzyme in the body. Two other derivatives, pyridoxal and pyridoxine are more active.

FUNCTION

Pyridoxal is the prosthetic group and functions as a coenzyme of several enzymes. It is codecarboxylase which decarboxylates tyrosine and other amino acids and is also a cotrans-aminase and a coenzyme with disulphurases. Pyridoxine is required to convert tryptophan to nicotinic acid.

No relationship has been established between this enzyme and anesthesia but its presence is so fundamental in ezymatic reactions that a knowledge of its activity is essential.

Ascorbic Acid (Vitamin C)

CHEMISTRY

Ascorbic acid (vitamin C, cevitamic acid) is a water and alcohol soluble vitamin which is available in synthetic form. The history of the discovery of vitamin C is common knowledge to all. The chemical structure resembles that of a monosaccharide. The vitamin is readily destroyed by heat and oxidation. Boiling, drying, or aging of the vitamin reduces its effectiveness. Vitamin C is easily absorbed from the intestinal tract and is distributed to all body tissues. The tissues with highest metabolic requirements appear to possess the greatest quantity. The lowest concentrations are reported in muscle and stored fat. The adrenal gland contains large quantities of vitamin C. Stimulation of the gland by the adrenocorticotropic hormone leads to depletion. Increased losses of the vitamin occur during high fever, particularly when bacterial infections are present. The vitamin may play a role in the reaction of the body to stress. Most mammals do not require an extrinsic supply of the vitamin since they have acquired the ability to synthesize it from their own tissues. Man, on the other hand, requires an exogenous source.

The blood level of vitamin C ranges from 1 mgm. to 2 mgm. per 100 cc. Values below 0.5 mgm. indicate deficiency. Amounts less than 0.15 mgm. are usually associated with scurvy which is attributed to the deficiency of the vitamin. A *renal threshold* of approximately 1.4 mgm. per 100 ml. of blood exists for vitamin C. Excess ingestion of vitamin C is secreted in the urine.

FUNCTION

Vitamin C is necessary for a number of essential body functions. Intracellular oxidation depends upon vitamin C. The vitamin is also essential for the formation of colloidal materials which are found in collagen, bones, and other skeletal structures. Vitamin C is essential for proper *healing of wounds* and has, therefore, recently assumed importance in surgery. Lack of vitamin C prevents fibroblasts from forming collagen and other forms of connective tissue. It causes weakness in the capillaries and in bones since the osteoblast requires it to form tissue. Vitamin C is essential for the formation of the intracellular cement. The permeability of the endothelium of the capillaries is decreased in deficiency states giving rise to hemorrhages in the skin and mucous membranes. Supplying the vitamin relieves the defect.

RELATION TO ANESTHESIA

Vitamin C may bear some relationship to anesthesia. Bowman and Muntwyler observed a marked increase in urinary output of vitamin C following ether anesthesia. Bartlett and Jones studied the vitamin C output in man but their data revealed that the increased output is not as striking as that seen in animals. Dilantin sodium administered to guinea pigs which had been on a vitamin C free diet but who were subsequently given ascorbic acid (5 mgm.) caused the ascorbic acid level to fall markedly. Three weeks were required for a return to normal. The level of vitamin C in spinal fluid is unchanged in chloroform and ether anesthesia in rabbits. In animals barbiturates (Nembutal) produces a more intense and severe hypnosis in vitamin C deficient animals. The hypnosis is reversed by the administration of vitamin C. Thiopental (Pentothal) did not behave similarly, however. It has been suggested that the mechanism of detoxification of thiopental does not require the vitamin C for completion while the pentobarbital does.

Lipoic Acid

This substance is a sulphur-containing fatty acid, 6, 8, dithiooctamic acid. The oxidative decarboxylation of pyruvic acid and keto glutaric acid involves both thiamine and lipoic acid as well as lipo- thiamide pyrophosphate. In its active state in the tissues lipoic acid is closely associated with thiamine pyrophosphate. Relationships to anesthesia have not been demonstrated.

Biotin

Biotin is a complex substance. It, too, is a member of the B complex. It is valeric acid with one of the hydrogen atoms of the terminal carbon substituted by complex ring called hexahydro-2 oxo,1, thieno, 3,4, imidazol. It is thought to function as a coenzyme in the "fixation" of carbon dioxide and takes part in the production of dicarboxylic acids to maintain the tricarboxylic acid cycle. Relationship to anesthesia has not been established.

Inositol

Inositol is hexahydroxycyclohexane. Together with choline it has a lipotropic action. It is also associated with the for- mation of inositol containing lipids. No relationship to anesthesia has been established.

Vitamin B₁₂

This vitamin is known as the antipernicious anemia factor. The exact structure has not been defined. It is believed to be involved in (1) the synthesis of labile methyl groups, (2) nucleic acid synthesis, (3) in the synthesis of methionine from homocystine, (4) possible roles in carbohydrate and fat metabolism. Relationship to anesthesia has not been established.

Metabolism and Anesthesia

DEFINITION OF METABOLISM

METABOLISM is a general term used to designate chemical processes occurring within the organism which supply energy for activity and vital body functions. The chief substances from which this energy is derived are carbohydrates, fats and proteins. These substances are composed principally of carbon, hydrogen, and oxygen. The energy results from oxidation and the end products are carbon dioxide and water. Oxidation is accomplished by a multitude of complex reactions aided by innumerable enzymes which are too numerous to be described here. Some of these enzymatic processes are influenced by drugs, including anesthetics. The oxidative processes occur in steps in many cases and may be halted at some intermediate phase and partially oxidized substances accumulate in the tissues. The oxidation of alcohol, for example, may be halted at the aldehyde stage by disulfuram (antabuse) instead of proceeding all the way to the terminal stage which yields carbon dioxide and water. The disulphuram inhibits one of the steps of intermediary metabolism and acetaldehyde accumulates in the tissues.

The utilization of *carbohydrate* by the organism yields 4.1 calories per gram, of *protein* 4.1 calories, and of *fat* 9.3 calories. The ratio of the volume of carbon dioxide liberated per unit of time to the volume of oxygen required for complete combustion is constant for a particular type of food substance. This ratio is referred to as the *respiratory quotient* (R.Q. $= CO_2/O_2$). When carbohydrate alone is consumed, the R.Q. is 1; when protein is consumed the ratio is 0.8 and fat, 0.7. The R.Q. serves as a clue to the type of food consumed. In an ordinary mixed diet, the R.Q. is approximately 0.85. *Heat production* bears a direct relationship to the oxygen consumed, the carbon dioxide excreted and the nitrogen eliminated. Heat production may, therefore, be computed from these three quantities if they are known. Heat production is expressed in calories per unit area of body surface per unit of time. Ordinarily it is expressed in calories per square meter per hour. The rate of heat production by the entire organism is known as the *metabolic rate*. Since the heat output varies widely with activity determinations are made at certain standard conditions referred to as *basal conditions*. The rate of heat output is known as the basal metabolic rate. The basal metabolic rate (B.M.R.) is the amount of heat released by a subject who is awake, in the post-absorptive state (fasting), at mental rest, and relaxed (lying down). The B.M.R. of a normal adult of approximately 25 years of age is 39.8 calories per square meter per

hour. This is the absolute figure. The B.M.R. is usually expressed in a relative manner in per cent deviations from normal. The B.M.R. of a subject producing the normal quantity of heat is expressed as 0%. Values in heat output above normal are expressed in per cent above the normal with a plus sign preceding them. A heat output of 43.6 cal./sq.m. per hour represents an increase of 10% above expected values. The B.M.R. therefore would be indicated as +10%. A heat production of 38.22 calories is 10% below normal and is, therefore, expressed as —10%.

VARIATIONS WITH PHYSICAL STATUS

The B.M.R. varies with age, sex, climate, and physical state of the subject. Metabolism is highest during infancy. The highest value is usually attained at the end of the first year of life. At this time the B.M.R. is approximately 50 cal./sq.m. The output gradually declines until puberty during which time an upward rise of several calories per sq. meter per hour occurs. After this the rate reverts to normal and maintains a plateau up to the age of 40 and then declines. After 40 a steady gradual decline occurs. The metabolic rate is decreased during sleep. The B.M.R. in females is approximately 7% less than that of males. During pregnancy, the overall rate increases due to the added metabolic activity of the fetus. The B.M.R. of the mother, however, does not change. Variations due to race and climate are negligible.

VARIATIONS DUE TO DISEASE

The B.M.R. is increased during fever (7% for each 1°F. rise), hyperthyroidism diabetes insipidus, cardiac decompensa-

tion, leukemia, anemia, essential hypertension and polycythemia. The metabolic rate is decreased in certain endocrine disturbances. Syndromes which cause hypofunction of the pituitary, thyroid or adrenal, such as Simmonds' disease, acromegaly or Addison's disease show a decrease in metabolic rate. The metabolic rate is decreased in starvation, malnutrition, and lipoid nephrosis. During innanition the metabolic rate may be as low as 40%. Metabolic rate is decreased during shock, deliberately induced hypotension and deliberately induced hypothermia. Considerable stress is often placed upon the relationship of metabolic rate to the tolerance to anesthetics, particularly the nonvolatile drugs. As a rule individuals whose metabolic rate is subnormal show decreased tolerance to anesthetics while the reverse appears to be true also in the case of increased metabolic rate. More is said of this later on.

DETERMINATION OF METABOLIC RATE

TECHNIQUES

Metabolic rate may be determined directly by measuring the total heat output in a calorimeter or indirectly by measured carbon dioxide excreted or oxygen consumed during a unit interval of time. Direct calorimetry is impractical and cumbersome for ordinary usage. The method, however, has been used to obtain basic fundamental and quantitative data from which metabolic rate may be computed indirectly from studies of oxygen consumption and carbon dioxide output. Indirect studies are employed for clinical medicine and research. The experimental error which is introduced is of little significance. Of the two indirect techniques the oxygen consumption

method is the simpler and more precise and yields the more reliable data. It is free from the vagaries inherent in the carbon dioxide method due to tendency to retain and store carbon dioxide, the buffering action with bicarbonates and loss by conversion to acid and excretion by the kidney.

APPARATUS

Various types of rebreathing devices (Sanborn, Krogh, and others) known as spirometers are employed to measure oxygen consumption. The devices employed for the tests are basically the same as closed circle rebreathing inhalers used for administering volatile anesthetics. The patient rebreathes for ten minutes from a closed circuit device which has been filled with a known volume of oxygen. After this time the volume of remaining gas is measured and the difference is used in the computation. The metabolic rate is then computed from tables prepared from data obtained by direct colorimetry, according to age, height, weight, and sex.

METABOLISM AND ANESTHESIA

Most of the data obtained over the years indicates that oxygen consumption is decreased during anesthesia. As a matter of fact several of the theories of narcosis have been predicated on this fact (Chap. 27). Some workers have reported opposite results but the bulk of the data favors, as one would expect, a decrease. Brewster and his co-workers, for example, found an increase in oxygen consumption in dogs during ether anesthesia. Possibly a release of epinephrine accounted for the increase in metabolism even though the animals were anesthetized. Orkin and his associates noted a shift in respiratory quotient during hypothermia but a decrease in O_2 consump-

tion. There is little other available data on the shift of the respiratory quotient during anesthesia. It is conceivable that the oxygen consumption of one organ may increase while that of another may decrease during anesthesia and that the sum total may be greater or less during anesthesia than in the waking state. However, the bulk of the evidence is against this. The generalization that has been made that the overall oxygen consumption falls still holds.

Oxygen consumption does increase during the induction of general anesthesia with ether, particularly if there is much excitement and muscular activity. Once full surgical anesthesia is established and a steady state achieved, the consumption falls to below the preanesthetic level. Oxygen consumption decreases during anesthesia with divinyloxide, chloroform, cyclopropane, thiopental and curare alone and in combination with anesthetic agents. McKesson and Clement reported a reduction in metabolic rate during ether, nitrous oxide, and ethylene anesthesia. Basal narcosis with avertin is also accompanied by a reduction in oxygen consumption. Schuberth observed a drop in metabolic rate in experimental animals (rabbits) during spinal anesthesia. On the other hand, in man the metabolic rate was found to be variable. Possibly this results from psychic influences, since the subjects studied were given no preanesthetic sedation. A decrease in oxygen consumption would be expected as a result of decreased muscle activity. Oxygen consumption is decreased during hypothermia. The decrease in oxygen consumption is due to a decreased utilization by the cells and not due to a decrease in availability. The arterial oxygen content remains unchanged or is even increased during anesthesia with

most agents. The A.V. difference remains unchanged or narrowed with most agents. During cyclopropane anesthesia, for example, the venous blood oxygen content is increased and the blood is arterialized. Although this suggests that cells use less oxygen, such data can be misleading because it does not take into account the rate of blood flow through the tissues. More is said of tissue utilization of oxygen later in the chapter.

PREMEDICATION AND METABOLIC RATE

Guedel stressed the importance of the lowering of metabolic rate by premedicating agents, particularly the narcotics, in facilitating induction of inhalational anesthesia. The decrease in oxygen consumption has been considered to be helpful when impotent drugs such as nitrous oxide are used. These drugs are used at partial pressures which normally cause the oxygen tension to be reduced below safe physiological levels. The use of the narcotic widens the margin of safety in regards to inhaled oxygen tension. It is more than likely that the benefits, whatever they may be, are derived from the additive effect of the narcotic with the gaseous agent and not the decrease in oxygen utilization.

Most of the evidence available indicates that metabolic rate is lowered when narcotics are used for premedication. Anderson, Stark, Waters, and others have reported a decrease in oxygen consumption following the administration of morphine in man. The decrease in oxygen consumption varies with the conditions of the experiment but ranges anywhere from 10% to 30%. Codeine causes a slight decrease in oxygen consumption. Evidence that other narcotics do likewise is also available. The com-

bination of morphine and scopolamine, and morphine and atropine administered subcutaneously are also followed by a decrease in metabolic rate. Morphine may act as a stimulant and raise oxygen consumption, particularly after the initial depression subsides.

The data concerning barbiturates are not striking and show discrepancies. These are apparently due to the dosage employed. Sedative and light hypnotic doses produce little or no change in oxygen consumption; heavy doses produce the expected depression of metabolic activity. Doses which produce sleep or severe depression cause a decrease in metabolic rate. Atropine (gr. 1/150) when used alone, with a hypnotic or narcotic causes slight increases in metabolic rate.

BASAL OXYGEN REQUIREMENTS DURING ANESTHESIA

Oxygen consumption during anesthesia varies from subject to subject. The usual metabolic requirement of an average size male adult (70 kg.) during anesthesia is approximately 250 ml. per minute. Patients having increased metabolic rates due to hyperthyroidism, fever and so on require a more than usual metabolic flow of oxygen.

CARBON DIOXIDE OUTPUT DURING ANESTHESIA

Carbon dioxide excretion, as is the case with oxygen consumption, is decreased during anesthesia. Most workers have assumed that the R.Q. is one and that, therefore, the output of carbon dioxide used equals oxygen utilization. The writer and his associates, while seeking data for studies of carbon dioxide absorption found, that the average output in adults during ether and cyclopropane anesthesia was 211 ml. per minute. The values ranged from 129 ml. to 425 ml.

The average for a group of non-anesthetized controls was 325 ml. The output was lower in females than in males and in patients in the older age groups it was less during ether than cyclopropane anesthesia. No differences in output were noted between patients premedicated with morphine and those premedicated with meperidine. The output during induction was variable. During maintenance, after a steady state is achieved, there is surprisingly little moment to moment variation in output. The average concentration of the total expired mass ranges between 4–5% in the anesthetized patients, and the minute volume averages 4 5 liters during spontaneous breathing. The total carbon dioxide excreted, nonetheless, is decreased. The higher exhaled concentration in the face of a decreased minute volume exchange merely indicates stagnation and incomplete elimination. All of this points to decreased production which is what one would expect in the face of decreased oxygen consumption. Nonetheless the possibility that carbon dioxide may be stored must also be entertained. Evidence of storage of carbon dioxide in bones and other structures has been presented by Rahn. The stored carbon dioxide is not immediately available for gaseous exchange. However, it is not unreasonable to suppose that this is not the case during anesthesia because a steady state develops, shortly after induction, which is unvarying.

BODY TEMPERATURE AND METABOLISM

Loss of Body Heat

Central nervous system depressants inactivate the heat regulating center and render the subject poikilothermic. The body temperature then tends to approach that of the environment. Heat is lost if there is a notable disparity between environmental temperature and body temperature. The temperature thus becomes subnormal. Heat is retained, if the disparity is not great, and it may be added if the environmental temperature is above body temperature. Heat is dissipated from the body by one or a combination of one or more of four physical processes—radiation, conduction, convection and by the evaporation of water from the body surface. During anesthesia a number of factors tend to combine to cause a fall in body temperature. (1) The heat output is decreased due to decreased metabolism. (2) Vasodilation occurs which increases the skin temperature and (3) external environment below body temperature. There are also factors which tend to add heat or favor its retention. Among these are anhidrotic drugs (atropine) which reduces evaporation, fever, and factors which add heat to the external environment such as operating room lights, hot packs, warmth from the bodies of operating room personnel and so on. Thermal equilibrium occurs when the sum of the calories resulting in heat gain or retention balance the sum of those resulting from heat loss. The fact that the environmental temperature is less than body temperature is not necessarily an indication that heat is not being retained and that hyperthermia may not occur.

Radiation

Heat loss by radiation accounts for only a small portion of the total lost by an anesthetized patient. The amount radiated depends upon the body surface exposed to the environment and the dif-

ference in temperature of environmental objects and gases and that of the body. Radiation is most effective when there is a great disparity between the body temperature and the environment and ceases when the environmental temperature reaches 33°C.

Convection

The loss of heat by convection likewise is not of any great significance since this is the heat lost to the environmental air. Gases have low specific heats and, therefore, absorb only small quantities of heat. For this reason large volumes are necessary for cooling or warming. Covering the body with drapes impedes heat loss through this avenue. Dissipation may be accelerated by forced convection, by means of air blowers. The heat loss is proportional to the square root of the air velocity.

Evaporation

Above 94°F. the greater portion of the body heat is lost by evaporation. At environmental temperatures of 75°F. or less evaporation plays a lesser role. The water for evaporation is derived from two sources, (1) by sweating and (2) by transudation. The amount which transudes is less than 10% of the total. Most of it is produced by sweating. However, when the sweating mechanism is inactive, as it frequently is during anesthesia, the water which transudes assumes a more important role. The most significant factor in evaporation of the water from the skin is the difference between the vapor pressure of the moisture on the skin to that of the surrounding air. The best guide in determining this is the wet-bulb reading. Relative humidity values may be misleading since the relative humidities may be the same at two

different dry bulb temperatures but the absolute moisture contents per unit volume of air vary considerably. Air at 40°F. having a 50% relative humidity holds less total moisture which exerts less vapor pressure than air at 80°F. which has a 50% relative humidity because it exerts less vapor pressure. Evaporation of water from the lungs normally dissipates approximately 10% of the expendable heat. The amount lost by warming the inspired air varies between 1 and 2%. This avenue of escape is of interest since loss may be hindered by the use of closed system inhalers. The amount of moisture lost by exhalation is less with closed systems than with open. More moisture is lost by using nonbreathing techniques supplying dry gas on demand than with rebreathing techniques. Heat is lost in open chest operations from convection and evaporation from the large moist surface which is presented to the room air.

Dissipation During Anesthesia

Orkin and Rovenstine studied the effects of anesthesia systems upon the dissipation of body heat in anesthetized surgical patients. They noted that the tendency towards elevation in body temperature was uncommon when the wet bulb temperatures were below 75°F. Above this temperature body temperature rose regardless of the anesthetic drug and type anesthesia system used. The to and fro system tends to add heat since the inspired air temperature ranges from 100–104°F. Inspired air temperatures in the circle systems are considerably less and more variable. They average between 88–92°F. The heat loss is less, but not startling in using the semi-closed non-rebreathing type of inhaler. Theoretically heat loss

should be higher using semi-closed inhalers but this does not appear to be so. As long as the environmental wet-bulb temperature remains below 75°F, little change in body temperature occurs using the circle system or high flow rates in non-rebreathing, semi-closed inhalers. Mechanical ventilators increase, to a degree, the loss of heat through the lung because greater volumes of gas are moved in and out of the lungs than are moved during spontaneous ventilation. The significant point to all this discussion is the fact that hyperthermia can occur even though environmental temperature is less than body temperature.

Since exposure of the anesthetized patient to temperatures above or below those of the body gives rise to hypo- or hyperthermia, some thought must be given to possible ill-effects which might ensue from such deviations. The effect upon various chemical and physical processes in the body may be quite profound. The effects on the viscosity of colloids, solubility of gases, electrolytes and metabolites and enzymatic activity may be deterimental if gross deviations in body temperature occur. Some of these effects are discussed later on.

The thinking concerning hypothermia has been reversed in recent years. Hypothermia is deliberately induced now where heretofore measures were taken to avoid it. More will be said about hypothermia later. Hyperthermia appears to be a more dangerous situation, particularly if the critical level of body temperature is exceeded. Once the rise in temperature is initiated the rise may proceed quickly to uncontrollable heights. An anesthetized patient in a hot, non-airconditioned operating room may develop a body temperature which may at times exceed that of the environ-

ment. Temperatures above 106°F. are critical and may lead to coagulation of cell protein and irrepairable damage of tissues. The cells of the nervous system are particularly susceptible. The subject retains the heat liberated, since the sweating mechanism is inactive and the temperature gradually climbs.

HYPOTHERMIA

Recently deliberate reduction of body temperature by exposure of anesthetized patients to near freezing temperatures has become a popular technique for decreasing metabolic activity of tissues. Such general body cooling is referred to as total body hypothermia. Other techniques associated with body cooling have also been introduced, most important of which are local hypothermia (or hypothermic anesthesia) and artificial hibernation. Total hypothermia is induced primarily to reduce metabolic activity in order that organs may be deprived of blood supply, without risk of death of tissues, for variable periods of time. Local hypothermia is designed to protect one area of the body from ischemia. Total hypothermia is discussed in detail further on.

HYPOTHERMIC ANESTHESIA

Hypothermic anesthesia is used to obtain pain relief by reducing the activity of nerve tissue. Nerve conduction ceases between 25° and 30°C. The sensation of cold is mediated by the end bulb of Krause while warmth is mediated by the end organs of Ruffini. Surface anesthesia may be induced by the application of cold to the skin by the use of ice, or by the evaporation of ethyl chloride, freon or other highly volatile liquids. The evaporation of such liquids often

produces temperatures far below 0°C. The skin freezes when the temperature falls below −3°C. Low temperatures produced by such evaporation may, therefore, result in frostbite. The cooling which occurs following superficial application of this sort is primarily in the skin because the tissues, since they are mostly water, conduct heat slowly and sufficient time rarely is permitted to elapse to sufficiently cool deeper structures. When deeper structures are to be cooled the limb is surrounded by ice for several hours. The anesthesia obtained is short lived—not longer than 30 minutes with this technique.

HIBERNATION

Hibernation may be true or "artificial." True hibernation can only be accomplished by animals endowed with the ability to decrease their temperatures. The heat regulatory center is inactivated and heat production is decreased. The body temperature falls to near freezing. The primary difference between hibernating mammals and non-hibernating lies in the ability to reverse the process quickly and warm the body by activating heat production and the *temperature control center*. Non-hibernating animals cannot *voluntary* rewarm when cooled. Artificial hibernation refers to the depression of the heat regulatory center induced by central nervous system depressants, such as chlorpromazine, the hypnotics and narcotics, which is then followed by spontaneous cooling. Unless environmental conditions are suitable so that heat is lost, the body temperature does not fall. Loss of heat is a physical process. No drug is available which accelerates heat conduction from the interior to the exterior of the body. Reliance for such depression in temperature must be solely upon rate of conduction and the gradient between the environmental temperature and body temperature. Placing the body in a warm environment after depression of the heat regulatory mechanism may result in retention of heat and elevation of body temperature. This has been discussed in the foregoing paragraphs.

A good deal of nonsense has been written about cooling the body by the use of drugs. The phenothiazines have been advocated for the purpose. No drug is capable of causing the rapid dissemination of heat from the body unless a cold external environment has been provided. The phenothiazines merely suppress the heat regulatory center and decrease activity. Heat is slowly lost to the environment by conduction, convection or radiation. The temperature falls only a few degrees when these drugs are used and does so slowly. The process of heat transfer is a physical one and not a pharmacological one.

TOTAL BODY HYPOTHERMIA

METHODS OF INDUCTION

Total body hypothermia is induced by a variety of techniques all of which absorb heat from the tissues in one way or another. Generally, the heat transferral is accomplished by conduction. The body may be immersed in water at 0°C., or is placed in contact with ice packs. The transfer of heat by this method occurs slowly and is not uniform due to the fact that tissues are mostly water and water is, relatively speaking, a poor conductor of heat. The heat transfer at 0°C. through a distance of 1 cm. in one minute is 0.00139 calories per sq. cm. area. A metal, for example, copper, has a transferral of

nearly 1 calorie under similar conditions. Cooling is attempted by blowing cold air against the body. The conductivity of air is far less than that of water, 0.000058 calories for each cm. distance per sq. cm. area per minute. Thus, convection which is sometimes utilized for cooling is a slower method yet. Air cooled to temperatures below the freezing point of water may cause frostbite because the outer layers of skin become supercooled due to the slow rate of conduction of heat from the interior to the periphery. Heat transfer in tissues is also retarded by the compartmentalization of water in the cell. This prevents mixing and diffusion so that conduction must be from cell to cell which delays the process still more. Cold also causes vasoconstriction which further retards heat loss from the skin.

The direct application of ice to the skin may cause frostbite if the ice is supercooled, as it frequently is, when removed from refrigerating units. This catastrophe may be avoided by immersing the subject in water mixed with ice and avoiding direct contact of the body with supercooled ice. An intervening film of water comes between the ice and the skin at all times.

RAPIDITY OF COOLING

It is customary when using surface cooling to reduce the temperature to 60% of the desired level. The temperature continues to drift for an hour or more after the coolant has been removed due to the interchange of heat between the superficial and deep tissues. More rapid cooling may be achieved by employing a cardiopulmonary bypass (artificial heart) and forcing the blood through coils surrounded by coolants. Total body cooling to 10°C. may be accomplished within 10 minutes using this technique.

Other methods of cooling consist of perfusion of pleural, peritoneal or intragastric surfaces with cold water. These are cumbersome and seldom used except for specialized indications.

REVERSAL OF THE HYPOTHERMIC STATE

As is the case with cooling, rewarming is a slow process. This again is due to poor conduction. The surface environment cannot be elevated beyond 108°F. otherwise the outermost tissues will be burned. Virtue and Swan suggest rapid rewarming by using diathermy intermittently. The electromagnetic waves penetrate into the tissues and are converted into thermal energy deep to the skin and over a wide area and in a greater bulk. Rapid rewarming may also be accomplished by warming the blood and perfusing the tissues by cardiopulmonary bypass.

METABOLIC RATE DURING HYPOTHERMIA

The object of hypothermia is to lower the metabolic rate of cell groups so that they may withstand ischemia or oxygen deprivation for longer than a few minutes. Numerous physical, chemical and biochemical alterations occur during the period of hypothermia. The heat output falls from the near normal value of 40 cal. per sq. meter of body surface per hour noted at 37° to 10 calories at 28°C. and 6 calories at 22°C. Normothermic subjects remove approximately 4% of the oxygen from the air they inspire. Hypothermic persons remove less than 2%. There is a corresponding decrease in carbon dioxide output. The R.Q. is shifted. The solubility of gases in blood and body tissues is increased. More oxy-

gen, nitrogen, carbon dioxide and anesthetic gas dissolve in blood at a given partial pressure. The oxygen dissociation curve is shifted to the left. However, oxygen is still supplied to the tissues as adequately as it is at normal temperatures. The speed of many chemical reactions is decreased. Enzymatic activity is decreased since many are operating below their optimum temperature. This is manifested by alterations in the clotting mechanisms, detoxification mechanisms, oxidative reactions and so on.

LIVER FUNCTION

The liver functions are sluggish. The oxygen consumption of the liver is 40% of normal. The excretion of bromsulphthalein is delayed. Bile formation is decreased. The glycogen content of the liver is reduced. These changes are all reversible however.

RENAL FUNCTION

The renal function appears to remain normal and is decreased only if the blood pressure is decreased. The chief disruption, if any, appears to be in the function of the distal tubule. The antidiuretic hormone does not influence renal tubule reabsorption as it does at normal body temperature. Creatine and ammonia production are reduced.

ENDOCRINES

The response of the adrenal to stress is impaired. The output of ACTH, 17 hydroxy keto steroids and other corticosteroids is suppressed. The output of epinephrine also is reduced.

NERVE FUNCTION

Nerve conduction is decreased in all fibres. The A fibres are blocked before the B and C—a situation opposite to chemical blockade. Sensation of touch is lost before pain. The action is potential in peripheral nerves is decreased, the duration of the spike is prolonged and the refractory period is decreased in a linear fashion with the decline in temperature. The autonomic nervous system remains active, since it is highly resistant to cold.

BODY TEMPERATURE AND DRUG ACTION

In vitro temperature has pronounced influence upon the rate of a chemical reaction. A chemical reaction in equilibrium according to the principle of Le Chatelier tends to shift in the direction which absorbs heat should additional heat be supplied to the system. It will, therefore, proceed with renewed activity in that direction until equilibrium is reestablished. On the other hand the shift in equilibrium will be to the side which evolves heat if heat is removed. There is ample evidence that this principle applies to chemical equilibrium in vivo also. Therefore, hypothermia may inhibit and hyperthermia accelerate certain biochemical reactions. Increases in body temperature tend to accelerate destruction of a drug and enhance its activity and toxicity while reduced temperatures do the reverse. However, this rule is not always applicable because other factors besides temperature and biochemical reactivity enter into the picture. Analyzing the mutual effects of drug action and body temperature is not as simple as it seems. A distinction must be made between body temperature and environmental temperature. Extreme changes in temperature, for example, may decrease the rate of absorption if a drug is given by other than the intravenous route. Cold causes vasoconstriction

which may often retard absorption. The delayed or decreased effect which results is not due to inhibition of the activity of the drug but to the restricted quantity available to the receptors. Elevation of temperature may accelerate absorption so that an enhanced response obtained would be the result of dose rather than alteration in reactivity.

Effects of Cooling

One would expect that cooling would inhibit activity of all drugs. This is not the case, however. Herman, for example, noted that the toxicity of pentobarbital, morphine and paraldehyde was increased over that at room temperature when rats were placed in an environment of 3°C. Gunther and Odoriz found the toxicity of caffeine was increased in frogs at lowered temperatures. Brown and Cotton noted that ouabain exerted less pressor effect in a heart-lung preparation at reduced temperatures and that the onset and duration of the effects were increased by hypothermia. Virtue has reported that vinyl ether administered to dogs during hypothermia causes liver necrosis in the post anesthetic period. The effects of tubocurarine are decreased during hypothermia due to a decrease in transport to the receptors resulting from vasoconstriction. On the other hand succinyl choline manifests increased duration of action due to a decrease in activity of the esterases by the reduction in temperature. These phenomena are reversed by rewarming. This data all indicates increased toxicity of a drug when temperatures are reduced.

Effects of Warming

On the other hand procaine is more toxic to mice made hyperthermic. Vasopressor amines such as ephedrine, propadrine and amphetamine manifest increased toxicity during hypothermia while the effects of Tuamine, Vonedrine and Privine are not significantly changed. The onset of action of most local anesthetics is decreased by warming. Mice show decreased sensitivity to hexobarbital and increased sensitivity to phenobarbital during hyperthermia. The former accumulates in the fat depots; the latter is distributed more uniformly throughout the body. This may account for the difference. It is apparent from the foregoing data that changes in temperature cause some sort of changes in reactivity and toxicity of drugs. No generalization can be made as to whether the response is one of augmentation or inhibition. What will happen cannot be predicted but can only be determined experimentally for each individual drug under a given set of fixed experimental conditions.

METABOLISM OF NERVOUS TISSUE

The metabolism of the organism as a whole is the sum total of the activity of each organ. It is well recognized that each organ is in a different state of activity depending upon the demands placed upon it by the rest of the body. It is also well recognized that the state of activity of each organ is not altered in a uniform manner. Little data is available on the effect of individual anesthetics on individual organs. The various components of the nervous system have received more attention than other organs. This is due to the fact that anesthetics have a special predilection for this system and that it withstands the effects of deprivation of oxygen and nutrients less than other tissues.

Nerve

The metabolism of peripheral nerves differs from that of brain. Tashiro demonstrated an increased carbon dioxide output from active nerve; Fenn called attention to an increased oxygen consumption; and Hill to an increased heat production. The heat, as is the case in active muscle, is produced in two stages. This suggests that nerve relies almost entirely upon carbohydrate for energy. Nerves contain glycogen and rely upon glycogenolysis for energy. A nerve excited in an anaerobic medium accumulates lactic and pyruvic acids but can conduct and recover in this medium without oxygen for a time before fatigue occurs. Nerve can, therefore, build up an oxygen debt. Hexoses, through the intermediary action of phosphocreatinine are the source of energy in active nerves. The metabolism is similar to that of muscle since lactic and pyruvic acids accumulate under anaerobic conditions. The initial heat is rapidly released and represents energy involved in the propagation of the impulse. The delayed heat output occurs during recovery which may occur 45 minutes later. The nerve may conduct under anaerobic conditions. The end products disappear slowly. The R.Q. of a *resting nerve* is approximately 0.8; that of an *active nerve* 0.9.

Brain

Brain contains some glycogen but utilizes the glucose circulating in blood for most of its energy. The R.Q. of brain is nearly 1.0. The oxygen consumption of brain varies with the part of brain studied. The cerebellar cortex consumes the greatest amount of oxygen; the cerebral cortex next. The central nervous system has a high metabolic rate and utilizes almost 10% of the total oxygen consumption of the body as a whole. Mental activity changes the oxygen consumption only slightly. The normal average oxygen consumption of brain is 3.3 ml. per 100 grams of brain. Approximate computations reveal that the oxygen dissolved in the brain is approximately 5 ml. per 100 grams, while not more than 2 ml. are dissolved in the brain itself. The normal rate of oxygen utilization is 46 ml. per minute. This total of 7 ml., therefore, would last less than 10 seconds if the supply were disrupted. In other words, the brain is unable to retain a reserve of oxygen. The situation is slightly different in regards to dextrose. As much as 2 grams of glucose or glycogen is available in normal brain. These stores render hypoglycemia a less acute problem than acute anoxia.

EFFECTS OF DRUGS

Cerebral metabolism may be decreased by depressant agents. These may be endogenous such as are found in acidosis (H^+, ketone bodies, fixed acids of uremia) or they may be exogenous as in the case of anesthetics. During narcosis with thiopental or ether cerebral oxygen consumption may be decreased as much as 40%. This occurs on the face of an adequate cerebral blood flow. Evidence has recently been introduced which indicates that the drugs do not act primarily on the neurons but interrupt synaptic transmission. Thus with synaptic transmission intact the neurons are in a state of greater than normal (tonic) activity. The depression in cerebral oxygen consumption is due to the decreased activity of neurons resulting from the release from tonic activity by the synaptic blockade.

Oxygen Consumption of Brain

Metabolism of brain in vivo is determined by measuring the A-V difference and the cerebral blood flow. The cerebral blood flow in man is measured by determining the uptake of nitrous oxide by the brain. Computations are made by using the Fick principle. Both the A-V difference and oxygen consumption are essential data in such a study. Oxygen consumption varies from one part of the brain to another. The white matter, which is similar to peripheral nerve, utilizes approximately the same amount of oxygen as peripheral nerve tissue. Grey matter, however, utilizes by far the greater portion of the total oxygen supplied to the brain. The blood leaving the brain through the jugular vein is about 60% saturated. This is less than that leaving most tissues and organs.

Respiration of the brain in vitro is determined in microspirometers by the methods of Warburg or Barcroft (Chap. 27). In vitro studies of brain tissues supply basic information of biochemistry of the brain, since it is only by such a study that the numerous variable factors which would enter into an in vivo study are eliminated. The brain probably utilizes only carbohydrate (glucose) in vitro. The bulk of the evidence obtained from in vitro cerebral studies (microspirometer studies) indicates that all depressants cause a decrease in oxygen consumption. Quastel and Wheatly observed a reduction in oxygen consumption and metabolite utilization by brain in vitro with most depressant agents. This depression roughly paralleled their anesthetic or hypnotic potency. However, one must bear in mind that the concentrations of drugs used were greater than those which clinically produce anesthesia and

that the changes observed may bear little resemblance to those occurring in intact human tissues.

LOCAL TISSUE OXYGEN CONCENTRATION

Methods of Determination

Localized tissue oxygen concentrations have been studied by measuring changes in oxidation reduction potentials by means of the *polarograph*. This device measures the oxygen present at a given locus by means of a polarized electrode introduced into the tissues. The oxidation reduction potential is an index of the amount of oxygen present at the site of the electrode. It is not necessarily a measure of the uptake of oxygen by the cell. Other less satisfactory techniques are available. They are more tedious techniques and give less accurate results They involve microanalysis of gases in a bubble, as a rule.

Polarography

The basic principle underlying polarography is as follows: An anode and a cathode are placed in a conductive aqueous medium containing two substances, one of which can be oxidized and one which can be reduced. A constant voltage flows through the solution. The rate of reduction of the reducible substance is directly proportional to the amount of current passing between the electrodes. The rate of reduction is in turn dependent upon the concentration of the reducible substance. Thus, a measure of the current is in essence a measure of the concentration of the reducible substance in solution. Oxygen is a reducible substance. When oxygen is dissolved in the solution, it takes on

two additional electrons which with water form hydrogen peroxide and two hydroxyl ions $(2H_2O + O_2 + 2E \rightarrow H_2O_2 + 2OH')$. *The voltage necessary to accomplish this is 0.3 to 0.8 volts.* The current flow, therefore, would be proportional to the concentration of oxygen in the proximity of the electrodes. The amount of current which flows is detected by a galvanometer and an amplifier which operates a direct writing oscillograph or other suitable recording device.

Polarographic methods have been in use for some time but the first true polarographic instrument was developed by Heydrosky and Shikata in 1925. This employed the dropping mercury electrode. *This type of instrument is no longer used* but modifications based upon the principle outlined above have been introduced and are in use. In 1953 Clark described a modification of the mercury electrode. In 1951 Glastone and Reynolds observed that a platinum wire could be substituted for the mercury cathode. Attempts to use this type of electrode in tissues were unsatisfactory because the electrode was in an environment of varying composition and subject to the changes in pH, temperature and so on which markedly influenced results. In 1953 Clark modified the electrode by enclosing a platinum cathode and a silver anode in various types of membranous sheaths which were impervious to liquids but which permitted the diffusion of gases. *The sheath is filled with a solution of an electrolyte which provides an environment of constant and unvarying composition for the electrodes. By use of this arrangement, it is possible to insulate the electrodes from the solutions of the body* but still permit the diffusion of gases into the protective solution of electrolyte enveloping the anode and cathode. The *Clark electrode has been used for analyzing oxygen tension in various tissues. Its usefulness, however, is limited for physiological studies because of its large size.* In 1958 Liston constructed a miniature electrode similar in principle to the Clark electrode, equivalent in size to a 20 gauge needle, which may be introduced into living tissues. The platinum cathode and the silver anode are insulated from each other and placed in a stainless steel sheath which serves as a needle. The tip of the needle is covered with a membrane, underneath which is a layer of 2% potassium chloride, which *is in contact with the end of the platinum and silver poles.*

UTILIZATION OF OXYGEN BY THE CELL

The cell is primarily concerned with using the oxygen which is present in the surrounding extracellular fluid. As a rule the quantity of oxygen present in fluids or gases, which is not combined with hemoglobin or other oxygen combining substances, is expressed in terms of tension. The cells are dependent not only upon (1) the tension of oxygen in the surrounding medium but also (2) upon the blood flow. *A constant uptake at a constant flow rate produces no change in local tissue tension. The tension falls when utilization of oxygen increases and rises when it decreases.* Decreased oxygen consumption and increased use of metabolites, and increased excretion of waste products, particularly carbon dioxide, has a vasodilator effect. The local utilization of oxygen then tends to regulate the blood flow through

most tissues. The circulation through the lungs and other organs is guided by the metabolic needs for oxygen. The vessels of the skin are exceptions. Polarographic studies show that profound changes in oxygen tension in tissues may occur rapidly. In vasodilated skin the oxygen tension is close to that of arterial blood. The oxygen tensions of skin follow those of arterial blood closely. A tension of four or five times that found when air is breathed is found when pure oxygen is inhaled. The tensions in tissues which use greater amounts of oxygen than the skin are not as close to those of skin nor do they parallel each other. The transfer of oxygen from the capillaries to the tissues is rapid but not rapid enough to be considered instantaneous. Data on tensions in heart, brain and muscle are scant.

EFFECTS OF ANESTHESIA

Green and his co-workers, using polarographic methods, studied the skin oxygen tensions in patients undergoing operation with cyclopropane-ether and thiopental-nitrous oxide anesthesia. The tensions were decreased during ether anesthesia but not with the other two agents. These studies, however, merely indicate the quantity of oxygen present. They neither indicate the tissue's ability to utilize oxygen nor the adequacy of the quantity of oxygen present in maintaining normal cellular function. Davis and co-workers noted that inhalation of pure oxygen causes sufficient vasoconstriction to reduce cerebral tissue oxygen tensions in dogs in the presence of hypocapnia and during hyperventilation.

TISSUE CARBON DIOXIDE TENSIONS

Recently methods have been developed for determination of carbon dioxide tensions in body fluids and tissues which obviate the objections and drawbacks of classical methods in use such as the Scholander or the Van Slyke apparatus. One of these is the Astrup method using a microglass electrode. The only readings necessary in this technique are the pH of the solution or blood under study. The principle is as follows: The microsample of blood is drawn into a microglass electrode. Only 0.025 ml. of blood is needed to fill the electrode. The sample is then equilibrated in tonometers with several samples of gas mixtures of known CO_2 tension and the pH is redetermined after equilibration with each gas sample. This data is then interpolated on previously plotted nomograms and CO_2 tension and CO_2 content are determined.

Base bicarbonate may be determined by adding lactic acid to the blood and converting the bicarbonate to free CO_2.

Electrodes are available which can be placed in the tissues or in blood. A telafon membrane separates a bicarbonate aqueous film from tissue fluid or blood. This membrane is permeable to CO_2 gas but not to ions which change the pH of the water film. The active surface is applied to tissue surfaces to measure tissue CO_2 directly.

The average CO_2 tension in cerebral cortex is 55 mm. Hg with arterial blood CO_2 at 55 mm. Hg. Values for liver, stomach and mucosa varied from 55 to 75. Skin when warmed rose to levels over 130 mm. Hg.

Detoxification and Elimination of Anesthetic Drugs

DETOXIFICATION

MANY DRUGS including anesthetics may, like other chemical substances, be subjected to biochemical mechanisms which are normally occurring in living tissues and be converted to new and, most of the time, physiologically inert substances. The biochemical conversion of a physiologically active chemical substance to one which is physiologically inert is termed *detoxification*. The terms *biosynthesis* and *biotransformation* are also used to indicate the conversion of drugs to new substances by the cells. The idea that the body has a multitude of defense reactions to noxious substances and that all detoxification reactions result in compounds of less toxicity is incorrect. Foreign substances undergo chemical transformation when they possess a structural group similar to a naturally occurring metabolite. They, thus, fit into an enzyme system which handles the metabolite which they resemble. The resulting compound may, therefore, be more detrimental than the original. The majority of detoxification reactions are concerned with organic compounds.

The term detoxification is occasionally used by clinicians to indicate the *reversal of activity* of one drug by another, such as the reversal of the narcotic effect of a barbiturate by analeptics, such as picrotoxin or metrazol. In this case, the analeptic merely adds its effect to the cell and alters the narcotic action without necessarily influencing the chemical destruction of the barbiturate. The use of the term in this sense is incorrect. The term detoxification indicates biochemical alteration of a substance. It *is not uncommon for biochemists to refer to the biochemical disposition of a chemical foreign to the body by the term metabolic fate.*

MECHANISMS OF DETOXIFICATION

A drug must be *reactive* in order to be detoxified. In order to be reactive, the drug must have a general configuration or specific group on the molecule which is susceptible to the various chemical processes which are occurring or *can occur in the body. Inert molecules,* such as those of cyclopropane, ethyl ether and halothane, undergo no change in the body. The subject of detoxification is complex. A variety of individual *chemical reactions occur to which reactive substances may be subjected in the organism. For the sake of simplification these may be grouped into four general categories of types of changes. These are* oxidation, reduction, hydrolysis and conjugation. The drug

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undergo a combination of several reactions before its final disposition. The fate of many drugs remains unknown. All the investigator may know about a particular compound is that it undergoes complete destruction within the organism with no clue as to the method of disposition. At times, it is obvious that the molecule is disrupted, particularly in the case of cyclic, large molecules. The term *degradation* is often used to describe this disruption of such molecules.

OXIDATION

Oxidation is the most important biochemical reaction occurring in the body since it is the source of energy required by the organism. It is not surprising, then, to find that certain drugs are consumed in this manner. The drug may be incompletely or only partly oxidized, but enough of a change is produced that it loses its chemical identity and physiological activity. It is not unusual for certain drugs to be completely oxidized to water and carbon dioxide. Primary alcohols are oxidized. Ethyl alcohol, is oxidized with the subsequent formation of 7 calories of heat per gram, carbon dioxide and water. Secondary alcohols are less readily oxidized. Tertiary and halogen substituted alcohols are oxidized with difficulty or not at all. Other mechanisms of detoxification are required for their disposition. Oxidation of the alcohol may proceed to the aldehyde stage and cease or go on to completion to the acid stage. Molecules with methyl groups are oxidized to carboxylic acids. The methyl group of the methyl butyl group on carbon 5 of thiopental is attacked by oxidation and converted to a carboxyl group. Aromatic hydrocarbons are slowly oxidized to aromatic alcohols (phenols):
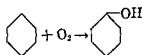
REDUCTION

Substances not oxidized may undergo *reduction*. Reduction refers to the addition of hydrogen to a molecule. Therefore, it is the reverse of oxidation. Electrons are lost from the compound undergoing oxidation which are gained by the oxidizing agent. The oxidizing agent is in turn reduced. Oxidation and reduction, therefore, occur hand in hand (Chap. 27). Chloral hydrate, an aldehyde, adds two atoms of hydrogen and is thereby converted to trichlorethanol, an alcohol.

$$R-\underset{\displaystyle O}{\underset{\|}{C}}-H + 2H \rightarrow R-\underset{\displaystyle OH}{\underset{|}{\overset{|}{\underset{H}{C}}}}-H$$

$$CCl_3-\underset{\displaystyle O}{\underset{\|}{C}}-H + 2H \rightarrow CCl_3CH_2OH$$
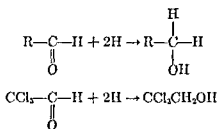
This, in turn, is detoxified further by other mechanisms.

HYDROLYSIS

Substances not amenable to oxidation or reduction may be subjected to *hydrolysis*. Hydrolysis literally means to break up or loosen by means of water. The cleavage results in the formation of an alcohol and an acid. Most local anesthetics are esters, some of which are easily hydrolyzed. Amides also undergo hydrolytic cleavage. Lidocaine, for example, is hydrolyzed to a certain extent in vivo. An amine and a carboxylic acid results in this type cleavage.

$$R{-}C{-}O{-}R_2 + H_2O \rightarrow RCOOH + R_2OH$$
$$\underset{O}{\|}$$

$$R{-}\underset{\|}{\underset{O}{C}}{-}\overset{H}{\underset{|}{N}}{-}R_2 + H_2O \rightarrow R{-}\underset{\|}{\underset{O}{C}}{-}NH_2 + R_2OH$$
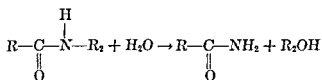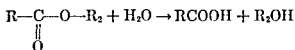
CONJUGATION

Compounds not susceptible to any of the three aforementioned mechanisms may undergo conjugation. Conjugation entails the addition of new side chains or groups to a molecule. A new compound forms which has altered physiological activity. Some foreign compounds are lipophilic. Conjugation converts these to hydrophilic substances which can be eliminated by the kidney. Usually an acid is used for conjugation. Quite often a strong acid such as sulphuric is used. However, a variety of radicals derived from organic acids, particularly amino acids, may be utilized. Acetic, aminoacetic (glycine), glutamic and glucuronic acid and cysteine, and ornithine are the more prominent acids used by the cell in biotransformation. Esters and glucosides usually form. However, many other types of compounds may form also. Glycine usually conjugates with a carboxyl group on cyclic structures, such as benzine, naphthaline, furane, pyridine, thiophene and on carboxyl groups separated from the benzine ring by a carbon atom (phenyl acetic) or a vinyl group (cinnamic acid). Benzoic acid becomes linked to the amino group of glycine to form benzoylamino acetic (hippuric) acid and water.

Acetic acid is frequently conjugated to aromatic amino acids. Sulphanilamide (para-amino benzine sulphonamide) is converted to acetylsulphanilamide by conjugation with acetic acid. Glutamine is used to detoxify phenylacetic acid. The conjugate which forms is phenylacetyl glutamine. The amino group is arranged in the same manner as that of benzoic acid in its combination with glycine. Cysteine is utilized in the detoxification of aromatic bromine derivatives of the type exemplified by brombenzine and hydrocarbons, such as naphthalene. Ornithine, an amino acid, is conjugated with benzoic acid by fowls. Sulphuric acid is conjugated to aromatic alcohols (phenols) to form esters known as *ethereal sulphates*. Indican or potassium indoxyl sulphate forms when phenol is detoxified by conjugation with glucuronic acid. Epinephrine and other aromatic amines similar to it are conjugated in this manner.

Conjugation with glucuronic acid is an important mechanism of particular interest to the anesthetist since a number of drugs he employs are detoxified in this manner. Chloral, tribromethanol and morphine are examples of conjugates of glucuronic acid. Glucuronic acid consists of a six-carbon chain with an aldehyde group at one end and a

$$\text{⬡—COOH} + \underset{\underset{NH_2}{|}}{CH_2{-}COOH} \rightarrow \text{⬡}\overset{O\ \ H}{\underset{}{C{-}N{-}CH_2{-}COOH}} + H_2O$$
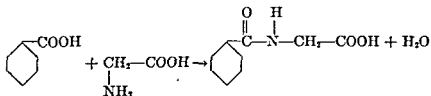
carboxyl group at the other end with one hydroxyl group on each of the intervening four carbons. Compounds with hydroxyl groups (alcoholic and phenolic) conjugate with glucuronic acid. Sugars are exceptions. Compounds with carboxyl groups attached to an aromatic nucleus also conjugate with glucuronic acid. Two types of compounds may form with glucuronic acid—those with an ester linkage and those which are glucosides. Acids may combine with the hydroxyl group next to the terminal aldehyde to form esters. Benzoic acid, in dogs, combines to form *glucuronyl monobenzoate*. Alcohols may join with the aldehyde group to form the glucoside type of linkage. The reaction with phenol results in the glucoside type of compound which is illustrated as follows:
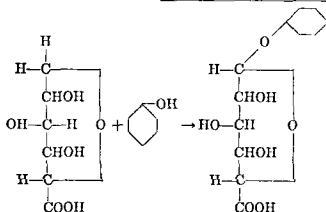
dine is ingested. This mechanism of detoxification is not common, however. Some texts consider acetylation and methylation as separate entities and divorce them from conjugation mechanisms.

Substances used for conjugation are obtained from endogenous sources within the organism. Glycine is synthesized in the body. Glucuronic acid is produced from the carbohydrate stores in tissues, probably glycogen. Insulin may hasten the production of glucuronic acid but the ingestion of free glucuronic acid does not accelerate conjugation of drugs ordinarily inactivated by this mechanism. Glucuronic acid is metabolized with difficulty and is even excreted into the urine in these circumstances. *Sulphuric* acid is derived from organic sulphur compounds in the body. When

The *halogenated aliphatic alcohols*, such as tribrom and trichlorethanol and morphine are also conjugated by the *glucoside* type of linkage (Chapter 15). The trihalogenated aldehydes, chloral and bromal, are first reduced to alcohols which are then conjugated with glucuronic acid.

Methyl groups may also be added as side chains to a cyclic structure. Methyl pyridium hydroxide forms when pyri-

overwhelming doses are taken, the body may not be able to provide enough of the conjugate and the organism is deprived of its minimal requirements. Therefore, symptoms of toxicity may arise from deficiency of such metabolites.

DEGRADATION

The mechanism of detoxification, referred to as *degradation*, is used to in-

dicate the transformation of compounds which occurs when the underlying chemical reaction is not understood and the end products are simple compounds, such as carbon dioxide, urea or water, and intermediate derivatives which cannot be identified. As more is learned about a compound said to undergo degradation it is generally found that it undergoes oxidation, reduction, hydrolysis or conjugation. In certain cases side chains responsible for physiological activity are removed from the molecule to form inactive compounds. The molecule as a whole may be completely disrupted into a number of compounds of smaller molecular weight. Cyclic structures may be stripped of their side chains by this mechanism. Compounds containing methyl groups become divested of these by the process known as *demethylation*. Caffeine (trimethyl xanthine) may be partly demethylated to di and monomethyl xanthines. Barbiturates, particularly the short-acting and the N-substituted derivatives undergo gradation by demethylation. Evidence exists that the pyrimidine ring of the barbiturates opens and the molecule is converted into various substituted amides which appear in the urine (Chapter 19).

COMBINATION OF REACTIONS

Frequently detoxification is accomplished in steps and a combination of mechanisms may be involved. Ethyl alcohol, for instance, is completely oxidized when ingested in small amounts. When quantities in excess of 10–15 grams per hour are ingested, the intake is greater than the quantity oxidized. Therefore, only a part is oxidized and the remainder is eliminated unchanged. An ester may first be hydrolyzed and the products of the cleavage then may

be oxidized, reduced, conjugated or altered by some other mechanisms. Acetanalid, for instance, is hydrolyzed into acetic acid and aniline. The aniline is oxidized and eliminated as aminophenol. The acetic acid is oxidized to carbon dioxide and water. Procaine is hydrolyzed to para-amino benzoic acid and diethyl amino ethanol. The para-amino benzoic acid is either methylated, conjugated with glycine or eliminated unchanged.

SITE OF DETOXIFICATION

The *liver* is the principal site of detoxification and detoxifies most drugs. Detoxification by the hepatic cell is performed by enzymes contained in the mitochondria. Hepatectomy or injury to the liver by chemicals is followed by incomplete inactivation and increased toxicity of many physiologically active substances. Other tissues and organs play a minor part in detoxification. Some drugs notably those which are conjugated with glycine are detoxified by the kidney. The plasma plays a role in detoxification since it contains enzymes such as hydrolases, oxidases and so on. Procaine, for example, is almost entirely detoxified (95%) in the liver in the dog; the remainder in the plasma. Chlorprocaine is hydrolyzed to a greater extent by plasma (5 times) than procaine. Data on detoxification of drugs by plasma may be misleading because some drugs undergo binding with protein. This inactivates the drugs temporarily but does not cause their metabolic destruction. Some drugs, as for example succinyl choline, are destroyed almost exclusively by the plasma. Only when large quantities are taken does the liver come into play. Spleen, muscle, brain, and spinal fluid play insignificant roles in detoxification. The chemical reactions of

detoxification are catalyzed by enzymes. Oxidases, peroxidases, esterases, dehydrogenases and many other enzymes found in the liver and blood aid in the detoxification. Epinephrine is oxidized by an aminoxidase found in blood and other tissues and is quickly inactivated. Succinyl choline is hydrolyzed by the plasma pseudo-cholinesterase. Certain of the enzymes present in blood, as for example cholinesterase, are elaborated by the liver. They are, therefore, deficient in plasma when hepatic insufficiency is present.

INFLUENCE OF CHEMICAL STRUCTURE

The manner in which side chains of a foreign molecule are attacked by the body, particularly side chains of aromatic compounds, depends upon the position of the radicals. The coupling of the carboxyl group of an aromatic acid with glycine is inhibited by the presence of another radical in the ortho position of the benzine ring. The nature of the radical influences the method of conjugation. Conjugation of a hydroxyl group with glucuronic acid on an aromatic nucleus is inhibited if a nitro or a halide group occupies the ortho position but is facilitated if this position is occupied by an amino group.

FORMATION OF TOXIC PRODUCTS

It has been mentioned previously that a deliberate detoxification is not attempted by the organism but rather that foreign substances possessing reactive groups are merely processed in a routine fashion by the naturally occurring biochemical mechanisms in the body. The drugs are handled in the same manner as substances necessary and common to body function. The physiological

inactivation is merely incidental and, under certain circumstances, a more toxic substance may form. Sulphanilamide, for instance, is converted into acetylsulphanilamide, which is more toxic than sulphanilamide. Aminophenol, which forms from the oxidation of aniline, is more toxic than aniline. Trinitrotoluene is converted by the body into dinitro hydroxyl aminotoluenes which are highly toxic. Other examples could be cited. The majority of detoxifications, however, yield products which are less toxic or physiologically inert.

SPECIES VARIATIONS

Studies of detoxification are difficult undertakings since many variable factors interfere with consistent results. One obstacle encountered in such studies is that mechanisms of detoxification vary with the species. In man, benzoic acid is conjugated with glycine to form hippuric acid, but in the dog it is conjugated with glucuronic acid to form an ester. Amylene hydrate is eliminated unchanged in man, while rats conjugate it with glucuronic acid.

EFFECT OF CONCENTRATION

The concentration of a drug in tissues distinctly affects the rate and mode of elimination. Short acting barbiturates in therapeutic doses do not appear in the urine because they are destroyed almost completely in the body. Should overwhelming doses be ingested they then appear in the urine, however. In such cases perhaps, detoxification cannot be maintained at the necessary pace, the renal threshold is exceeded and the drug passes into the urine. Large doses of certain drugs inhibit general metabolism so that the biochemical processes are reduced below the normal level and de-

toxification is inhibited. Phenol in small amounts is rapidly detoxified. In lethal amounts the transformation is inhibited because it inhibits metabolism.

VARIABLE FACTORS INFLUENCING DETOXIFICATION

The routes employed and the rates of administration of drugs may influence their excretion and destruction since they cause variation in the concentrations in blood and tissues. Drugs given orally or rectally pass directly to the liver. Their rate of destruction may differ from the rate of those given intravenously. Succinyl choline is ineffective orally but effective intravenously. Other factors, such as *tolerance* to a drug, *metabolic rate, state of nutrition of the organism, state of hydration, environmental temperature, body weight, body surface, sex, age,* and *body temperature* may influence destruction and elimination of a drug. The destruction and elimination of morphine is different, for example, in the addict and the non-addict.

METHODS OF STUDY OF DETOXIFICATION

A number of methods are available for the study of the physiological inactivation of drugs—the *direct,* or *chemical method* and the *indirect,* or *pharmacological* method.

DIRECT METHOD

Tissues, body fluids, and other biological preparations must be examined quantitatively by chemical methods for unchanged drugs or products of detoxification. *Microchemical* methods are often necessary when the quantities involved are minute. The concentration of drugs is reduced to almost an infinitesimal level in the case of non-volatile types, such as the alkaloids, which are administered in fractions of a milligram to subjects weighing many kilos. The detoxified product is often difficult to isolate and identify. Frequently, experimenters have resorted to *perfusion experiments* to study chemical changes. Under these experimental conditions complete recovery of the initial amounts of the drug is possible. Systems of this sort in which drugs are added to excised tissue in vitro, even *though the tissues are living,* are artificial, however, and one cannot unreservedly apply findings to man.

INDIRECT METHOD

Chemical methods for analysis of newer drugs are not available or practical. Experimenters, therefore, must resort to the indirect or *pharmacological methods* for data. In these cases, the drug under investigation is injected into a selected experimental animal in doses of sufficient amount to produce the desired physiological effect. Following this, at given intervals, as the effect subsides, *fractions of the original dose are* re-injected in amounts sufficient to restore the original level of pharmacological response. The object of such injections is to replace that portion of the original dose which has been inactivated by the tissues in the stated time interval. The longer the time interval from the moment of original injection, the greater will be the replaced fraction. Eventually, the original dose is required to reproduce the response. At this point complete desaturation will have occurred. Curves of the rate of inactivation of a drug may be plotted from successive experiments of this sort. Kohn-Richards, using the pharmacological method, has studied the destruction of barbiturates

and has derived mathematical formulae from his experimental data which may be used to calculate the rate of inactivation of a drug. Tatum and others studied the inactivation of stimulating drugs, such as picrotoxin, metrazol, and coramine, by the indirect method, also. The biochemical mechanisms concerned in such inactivations are not known exactly, but the organ and tissue involved and the rate of excretion of unchanged drugs may be determined.

Some observers have studied the inactivation of drugs by incubating them in vitro with various excised tissues, such as plasma, liver, kidney, muscle, and spleen. The undestroyed fraction is extracted and injected into animals to obtain the effect characteristic of the drug. Data from such studies, though useful, are not necessarily applicable to the intact animal or to man.

FATE OF NONREACTIVE DRUGS

Nonreactive drugs, whether volatile or nonvolatile, are eliminated from the body *unchanged*. The elimination of nonreactive substances is of vital importance and interest to the clinician because the majority of the inhalation anesthetic drugs are nonreactive. *Elimination of* these substances depends almost wholly upon volatility, diffusibility, solubility, and other physicochemical factors.

NONVOLATILE DRUGS

Nonvolatile, nonreactive drugs are eliminated through the *kidney* and to a lesser extent the *gastrointestinal tract* and *skin*. The *elimination by the kidney* may vary with the plasma concentration of the drug, the blood flow through the kidney, glomerular filtration, threshold level of the drug (if it has one), and the degree of tubular excretion. Although the

matter is controversial, some investigators feel that certain drugs, the barbiturates, for example, are threshold substances. The shorter-acting barbiturates do not attain the threshold level since it is high and for this reason do not appear in the urine. Longer-acting homologues are believed to have a low threshold and are eliminated by the renal route.

The solubility of many substances varies with the hydrogen ion concentration of the dispersion medium. A substance may be soluble in the alkaline medium provided by the plasma. However, as it passes through the kidney into the distal portion of the convoluted tubule where the urine becomes acid, the same substance may be precipitated due to the decreased solubility. Some of the recently introduced chemo-therapeutic drugs of the sulphonamide type precipitate in the tubules and cause a decrease in renal function, or even anuria. They may also form calculi and block the pelvis of the kidney. None of the currently-used nonvolatile, anesthetic drugs is known to behave in this manner in therapeutic doses. However, *diuresis* may increase the output of substances normally excreted by the kidney. Alcohol, paraldehyde, the barbiturates, and other drugs may be eliminated in greater amounts if a diuresis is induced by drugs or infusion of liquids.

VOLATILE DRUGS

Volatile drugs, although eliminated by other channels also, are excreted chiefly through the *lungs.* The elimination of inhalation anesthetic agents by the pulmonary route is the *converse* of absorption. One can, therefore, consider the laws governing both processes simultan-

eously. These have been mentioned in detail in Chapter 4.

DISTRIBUTION OF NONVOLATILE DRUGS

The *distribution of nonvolatile anes-thetic drugs* in the body depends upon their rate of administration, dosage, and rate of absorption. Intravenously, orally, rectally, and intramuscularly adminis-tered drugs are carried to the right heart and mixed there with other venous blood and then distributed to tissues. Inhaled drugs are carried by the arterial blood directly from the lung to the tissues. Drugs administered orally and rectally are absorbed into the portal venous sys-tem and pass through the liver. Whether or not any difference is effected by this preliminary passage through the liver is not known. Distribution in tissues may vary with the time interval fol-lowing administration. Immediately after injection of a drug, the liver, intes-tines, and spleen may contain consider-able amounts. After a time there may

be a distribution to the brain, kidney, or muscles, depending upon the solubility and particular affinity it has for the tis-sue. Barbiturates, halogenated alcohols, local anesthetic drugs, and opium alka-loids diffuse into nervous tissue since they, too, are lipoid soluble. The distribu-tion of these in tissues is discussed under *individual drugs*.

Saturated and unsaturated hydrocar-bons are inert in vivo. Aliphatic alcohols are usually oxidized, or eliminated unchanged. Halogenated hy-drocarbons are eliminated unchanged. The halogenated aldehydes and al-cohols are usually conjugated with glu-curonic acid and eliminated through the kidney. Esters are hydrolyzed. Local an-esthetics and certain of the muscle re-laxants (succinyl choline) come under this category. Long-acting barbiturates are eliminated into the urine; the short-acting type are detoxified by the liver. Usually they are oxidized at the side chain. Then the ring is opened and the drug is converted to urea and water.

Toxicology

UNTOWARD RESPONSES TO ANESTHETICS

FATALITIES AND INJURY TO TISSUES occasionally ensue from the use of anesthetics or drugs used as adjuncts to anesthesia. More often than not the drug is incriminated—justifiably in some cases and in many cases not. All anesthetics are protoplasmic poisons, and, if used to excess, cause death or injury to cells. However, overdosage should not be the only factor incriminated. Products of deterioration or contaminants often cause responses not ordinarily anticipated of a pure drug. Trichlorethylene, for example, may be contaminated with dichloracetylene, a product resulting from deterioration and oxidation. This substance causes neuritis of the cranial nerves, particularly the fifth (anesthesia). Allergic responses, mal-administration and causes incidental to administration and not related to the drug may also be responsible for unanticipated reactions. Untoward responses so produced may, on occasions, assume medico-legal importance. Evidence based upon toxicological examination may be helpful in many instances to clarify matters. It behooves the anesthetist, therefore, to be familiar with the rudiments of toxicology, so that this line of investigation may be utilized to its fullest advantage.

SCOPE OF TOXICOLOGY

Toxicology is the study of identification of poisons and since poisons are chemicals toxicology is a specialized branch of analytical chemistry. The scope of toxicology, however, is somewhat broader than that of analytical chemistry. The quantities of drugs which are dealt with in toxicology are so minute in some cases that they are not detectable by chemical methods. Suitable tests are either unavailable or not sufficiently sensitive to be reliable. In some instances bio-assay techniques are used while in others physical methods of analysis have been developed. Toxicology also embodies a knowledge of biochemistry and pharmacodynamics as well as chemistry. The mode of absorption of a suspected drug, its distribution in the body and manner of elimination must be understood to avoid pitfalls. A knowledge of the systemic and local effects of an offending agent together with possible anatomic change, both gross and microscopic is necessary. Thus, the history of the illness caused by the poison, duration, symptoms and progress of the patient must be studied. Specimens removed from the body must be examined and subjected to toxicological analysis.

COLLECTION OF SPECIMENS

The materials usually removed from

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the body for examination are: (1) *Body fluids* (urine, cerebrospinal fluid, blood and gastro-intestinal contents). These may be obtained ante mortem or post mortem. (2) *Organs* or sections of tissues (hair, skin, bone, and cartilege, etc.). (3) Specimens of *unused portions of the drug*. Solvents used for preparing solutions, utensils used in preparation which may have possibly contaminated the drug. The container in which the drug was delivered should be saved and inspected. The apparatus or device used for administration may yield useful clues. For example, soda lime used during closed circuit anesthesia using trichlorethylene may contain products of decomposition of this agent. Syringes used for injection of a drug may have been *contaminated by detergents. They* should be held until examined.

Specimens should be examined and *tested as soon as possible, particularly* when the suspected agent is known to be unstable. Body fluids and tissues should be properly preserved if it is not feasible to analyze them promptly. Drugs may be altered in cadavers and other biological material. The embalming fluid may interact with the suspected poison or interfere with tests for it.

ANALYSIS OF GASES AND VAPORS

Gaseous agents and vapors of volatile liquids may be readily lost from the specimen. Specimens containing volatile drugs, therefore, should be refrigerated and stored promptly in airtight containers to minimize such loss. Generally the quantitative analyses of organs *containing gases is unsatisfactory because one* is never certain of the quantity lost in handling *the tissue before analysis.*

However, blood, urine and spinal fluid may be analyzed with precision if the specimen is collected and preserved anaerobically. Usually a preservative is added to prevent decomposition of biological and pathological specimens. Formaldehyde, phenol, chromic, picric acid and other fixatives are used by pathologists for routine examinations. These should be omitted if the specimen is used for *toxicological analysis* because these agents may combine with the drug and interfere with the analysis or give false positive reactions. Often in these cases reliance is placed upon refrigeration. In some cases a preservative is *necessary to inhibit destruction of the drug* by bacteria or enzymes present in the tissues. Procaine, for example, is quickly *hydrolyzed by the blood esterases un-less an enzyme inhibitor, such as potas-sium arsenite is added when the blood is collected.* When the use of a preservative is mandatory one should be selected which does not respond positively with contemplated tests. Preservation is also necessary because decomposition of naturally occurring constituents of the body, such as proteins, fats, and carbohydrates may yield substances which react with the reagents and give false positive tests. Various amines, once referred to as *ptomaines,* result from the decomposition of proteins. These may respond positively to tests which are based upon detection of amino groups.

SELECTION OF MATERIAL FOR ANALYSIS

The selection of the proper organ or fluid to be examined is important. This *depends largely upon the chemical and physical nature of the suspected drug* and the manner in which it is distributed in the body, its mode of detoxifica-

tion and the period of time which has elapsed after the drug has been ingested before the examination is undertaken. Anesthetics and other central nervous system depressants are distributed principally in nervous and lipoid tissues since they are lipophilic. Tissues from the central nervous system, therefore, are more likely to contain the drug. Some volatile drugs, such as ether and chloroform are, relatively speaking, soluble in water. After anesthesia has progressed for some time they are found in appreciable quantities in the "watery" tissues of the body. Non-volatile drugs used for anesthesia or hypnosis are for the most part water soluble. Therefore, they too are found in the "watery" tissues of the body, particularly early after administration. Later, since they also have some lipoid solubility, they pass into the brain and adipose tissues where they may be detected for some time after they have disappeared from the viscera. Thiopental, for example, quickly passes into the brain and into the watery tissues. Equilibrium is established with plasma within a few minutes. The adipose tissues have a high affinity for the drug but, since the blood supply to these tissues is sparse, the uptake is delayed and the concentration does not reach its maximum until an hour or so later. At this time the concentration in adipose tissues may be fifty times greater than in muscle. Therefore, one organ or tissue may have sizeable quantities early after administration and little or none hours later while a tissue which has none early may be saturated later. Generally the liver, spleen, kidney, adrenal, adipose tissue, brain, portions of the gastro-intestinal tract and lungs are the organs examined for drug content. Liquids of low volatility which are excreted in part by the lungs may be

detected there. Non-volatile drugs are not found in the pulmonary tissues. The analysis of lungs for gases or vapors of highly volatile liquid anesthetics is not satisfactory. Evidence of irritating and necrotizing contaminants in inhalational agents, as for example, phosgene, may be detected in the lung. The *liver* is always examined because this organ not only detoxifies most drugs but is one of the first to receive them after absorption from the gastro-intestinal tract and the portal system. The kidney likewise is always examined because this organ excretes both the unchanged drug and any detoxified products. The stomach and intestines and their contents are examined not only when the drugs have been administered orally or rectally but also by other routes. Some drugs are eliminated into the gastro-intestinal tract or into the bile even though administered parenterally and can, therefore, be isolated there. Morphine, for example, may be excreted into the colon. Some drugs are poorly absorbed from the intestinal tract and may be detected in appreciable quantities in intestinal contents hours after administration. Others are rapidly absorbed and are barely detectable shortly after administration. Almost 95% of a dose of tribromethanol is absorbed from the colon within the first 30 minutes.

VALUE OF GASTRIC LAVAGE

In poisoning or when overdosage is suspected, it is customary to lavage the stomach and, at times the colon, with saline or solutions of antidotes which oxidize, precipitate, neutralize or adsorb the poison. When the offending agent is an alkaloid the stomach is lavaged with a dilute potassium permanganate solution which acts as an oxidizing agent and renders the compound physiologically in-

active or with a suspension of activated charcoal which acts as an adsorbent. Acid drugs are neutralized with sodium bicarbonate or calcium carbonate. Alkalies are neutralized with weak acids, such as dilute acetic (vinegar), or citric (lemon juice). The action of caustic agents which coagulate protein may be nullified by the prompt administering of egg albumin.

The value of gastric lavage in cases of poisoning has been questioned. Unless the stomach is evacuated shortly after ingestion a drug passes quickly into the intestine, where the bulk of the absorption occurs. Lavage is of little benefit once the drug moves into the intestines. The possibility of aspiration in attempting lavage in comatose patients may offset the benefits dervied from this procedure.

VALUE OF BLOOD ANALYSIS

Blood analyses are extremely important in many cases. Blood for analysis may be obtained from the heart immediately after death before post mortem clotting occurs. Blood should be refrigerated or treated with sodium arsenite or other enzyme inhibitors to prevent destruction of the drug by the enzymes or bacteria. Undue reliance is often placed upon blood levels. In some cases blood analyses are valueless. A barely detectable blood level may be obtained in the face of a high tissue level. A negative result may be due to intravascular breakdown of the drug. Minute traces of certain drugs continue to be present in blood for hours after conclusion of anesthesia. This is due to the fact that some drugs are stored in lipoid tissues and pass from these storage depots slowly because of the poor blood supply. The bulk of cyclopropane disappears from

the blood within 10 minutes but minute traces may be detected in the blood for several hours after termination of anesthesia. This persistent trace represents that fraction which passes from the adipose tissue which releases it slowly due to the poor blood supply and the high affinity of the fat for the drug. Blood which contains drugs which are bound to protein may fail to respond to tests for their identification. Blood levels, therefore, are low or zero.

Slowly diffusible drugs, as for example the quaternary bases, exemplified by d-tubocurarine, may give high plasma levels immediately after injection and low blood levels after the drug has diffused into the interstitial spaces. A drug may be absent from the blood stream but still may be present in sufficient quantity at a particular receptor site to produce its usual pharmacologic response. Succinyl choline, for example, is rapidly hydrolyzed by the plasma. A quantity sufficient to cause depolarization passes into the myoneural junctional tissues where it is not attacked by the enzyme. Thus, a paralytic concentration may be present in the receptors while undetectable amounts are present in the plasma. The correlation between degree of nervous system depression and blood level is more striking with the inert inhalational anesthetics than with nonvolatile drugs. The bloods levels in this case reflect accurately the state of depression. This is not so with the nonvolatile drugs.

URINE CONCENTRATIONS

Data obtained from concentrations of a drug in urine may be misleading. Some drugs are detoxified so completely that they do not appear in the urine in detectable amounts. Succinyl choline and

thiopental, for example, follow this pattern. Slowly diffusible substances do not appear in the urine until hours after the physiologic effects have disappeared. The quaternary bases pass from the vascular space into the interstitial fluid spaces from which they are removed by glomerular filtration. Certain drugs do not pass into the urine after therapeutic doses, but spill over when massive doses are injected and the plasma level exceeds the renal threshold. Below this level detoxifying mechanisms handle the elimination in its entirety. Above threshold levels the drug spills into the urine. Secobarbital behaves in this manner.

ANALYSIS OF CEREBROSPINAL FLUID

Analysis of cerebrospinal fluid may be helpful when the intrathecal, peridural or paravertebral route of administration has been utilized. When other routes of administration have been used the concentrations may parallel plasma levels. In some cases the concentration may equal plasma level, in other cases it may be half; in other cases the drug is absent from the spinal fluid. There is no relationship between cerebrospinal fluid concentration and brain content of drug. When massive doses of barbiturates have been ingested the brain content may be appreciable, but the cerebrospinal fluid content is negligible.

PLAN OF TOXICOLOGICAL ANALYSIS

The usual procedure for identification of an unknown substance is to isolate it so that it may be subjected to the contemplated method of analysis. Unfortunately, specific tests which unequivocally identify a substance are not available for many of the drugs encountered in toxicology. Therefore, a plan of analysis is followed in which the drug is first "pigeon holed" into a certain category. This is accomplished by studying its physical and chemical properties, such as melting and boiling point, solubility in water and organic solvents, reactions to acids and bases, crystalline structure, odor, stability towards heat and so on. A discussion of more than the highlights of the plan of analysis which is followed in the toxicological examination of a suspected substance is beyond the scope of this book. The reader is referred to more detailed texts for amplification of the subject.

CLASSIFICATION OF POISONS

Poisons are usually grouped as (1) inorganic substances and (2) organic substances. Most drugs used in anesthesiology are organic substances. Inorganic substances are of far less interest to the anesthesiologist than organic; therefore, they will be slighted in this discussion. Organic substances are grouped as volatile and non-volatile. The non-volatile group includes aliphatic substances, amines, amides, alkaloids, synthetic substances related to alkaloids, amaroids, glucosides and so on and other substances. Inert gases and anesthetics, such as nitrous oxide, cyclopropane, ethylene or vapors of highly volatile liquids, such as ethyl chloride are difficult to recover from tissues because they quickly diffuse and pass off after specimens are exposed to air or they are present in such small quantities that their detection and determination is not only a difficult undertaking but futile, as a rule. However, gases which enter into combination with tissue constituents, such as carbon monoxide, may be recovered quantitatively

in blood. A sample of the suspected inhaled atmosphere may be subjected to analysis if it is available.

ANALYSIS OF DRUGS OBTAINED FROM TISSUES

If the specimen consists of tissue, approximately 500 gms. are minced and suspended in water in a suitable flask connected to a cold water condenser. The mixture is acidified with an organic acid which does not precipitate proteins, usually lactic or tartaric. The volatile substances are separated from the nonvolatile by fractional distillation. Steam is passed through this mixture and the distillate collected in fractions (Fig. 1. 38). Three or four fractions at various temperature levels are collected. Some drugs are more volatile than others and, therefore, appear at different stages of distillation. The highly volatile agents, such as vinyl ether, aldehydes, ketones and halogen compounds appear in the first fraction. They are collected in a closed receptacle surrounded by "dry ice" or in one containing a solvent or other reagent which will bind or dissolve all of the distillate and prevent loss. The less volatile, higher boiling substances appear in the subsequent higher boiling fractions. After this initial distillation with the acid, the mixture is made alkaline with sodium hydroxide and the fractional distillation is repeated in a similar manner. Volatile basic substances, such as amines and quaternary bases are liberated by the alkali and distilled over in this fraction.

The *distillates* are treated with various reagents which serve to identify the suspected constituents. Generally, some clue regarding the chemical nature of the suspected poison has been provided. The toxicologist then is able to narrow the number of tests he must employ down to a few or, in some cases, even one. If the nature of the substance is completely unknown to the analyst its behavior to oxidation, reduction, hydrolysis, diazotization, deaminization, precipitation and other reactions must be studied and this data correlated with physical factors.
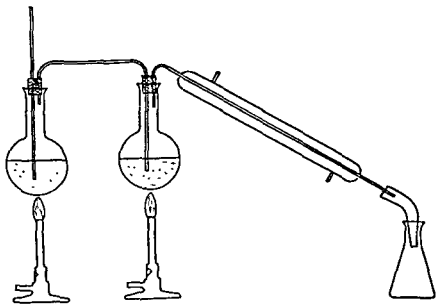
FIG. 1.38. Steam distillation apparatus.

EXTRACTION OF DRUGS FROM TISSUES

The extraction of non-volatile substances from tissues can be a tedious process. Many techniques have been devised to accomplish this extraction. Fundamentally, all these techniques are alike but differ from each other merely in details. The Stas-Otto process, for example, recommends that the finely divided, ground tissue be extracted in two to three times its volume of absolute alcohol. The mixture is heated on a water bath until reduced to a thin syrup. Water is then added, and the precipitate which forms is filtered. The filtrate is evaporated to dryness. The residue is then dissolved in water, acidified, and extracted first with hot chloroform, ether, benzene or other organic solvents, depending upon the nature of the suspected material. The first extraction removes chloroform-soluble and acid substances, such as barbiturates or phenols. Then ether-soluble, then benzene-soluble substances are removed. The substrate is then made alkaline and extracted once again with chloroform, ether or other solvents which appear to be indicated. Basic substances, such as the amines, quaternary bases and alkaloids are extracted in this step. Benzene, petroleum, ether, amyl alcohol and other solvents are used when the suspected drug is known to be insoluble in chloroform or ether. The extracts are then evaporated to dryness and the residue subjected to appropriate tests, such as melting point, oxidation, reduction, hydrolysis and so on. The drug may be purified by crystallization, sublimation or distillation in vacuo and then subjected to quantitative determinations by gravimetric, volumetric, colorimetric, fluorimetric, paper and gas chromato-graphic, electrophoresis, bio-assay or other techniques of analysis.

PREPARATION OF TISSUES FOR ANALYSIS

Tissues are usually ground with a food chopper so that they are finely minced before extraction with the solvent. Some workers freeze the specimen with liquid air, pulverize the mass and then extract with the desired solvents. Digestion by enzymes, such as pepsin, trypsin, or caustic chemicals is occasionally necessary to macerate tissues. These methods are satisfactory only if the drug in question is known not to be altered by these substances. Bones and joints may be crushed and extracted in the same manner as other tissues.

DIRECT ANALYSIS OF SPECIMENS

Urine, spinal fluid, and *fluid from serous cavities* containing no protein may be extracted directly with appropriate solvents after being reduced in volume by evaporation and treated with copper sulphate, silica, and other agents to remove pigments. Blood and other protein containing fluids may be treated with phosphotungstic acid or other protein precipitating agent and the filtrate subjected to the usual extraction procedures for analysis with the usual chemical and physical tests. Tablets, powders, contents of capsules and unknown liquids are dissolved, diluted with water and then extracted with appropriate solvents.

SUMMARY

It can be seen from the foregoing discussion that toxicological analysis can be a complex procedure to be done only by skilled, informed persons. The anesthesiologist may be helpful by properly collecting material for analysis.

APPENDIX

APPENDIX: TABLE I

INTERNATIONAL ATOMIC WEIGHTS

	Symbol	Atomic Number	Atomic Weight		Symbol	Atomic Number	Atomic Weight
Aluminum	Al	13	26 97	Molybdenum ...	Mo	42	95.95
Antimony	Sb	51	121 76	Neodymium ...	Nd	60	144.27
Argon	A	18	39.944	Neon	Ne	10	20.183
Arsenic	As	33	74 91	Nickel	Ni	28	58.69
Barium	Ba	56	137 36	Nitrogen	N	7	14.008
Beryllium	Be	4	9 02	Osmium. ...	Os	76	190.2
Bismuth	Bi	83	209 00	Oxygen ...	O	8	16.0000
Boron	B	5	10 82	Palladium ...	Pd	46	106.7
Bromine	Br	35	79.916	Phosphorus	P	15	30.98
Cadmium	Cd	48	112 41	Platinum	Pt	78	195.23
Calcium	Ca	20	40 08	Potassium	K	19	39.096
Carbon	C	6	12.010	Praseodymium	Pr	59	140.92
Cerium	Ce	58	140 13	Protactinium .	Pa	91	231
Cesium	Cs	55	132 91	Radium	Ra	88	226.05
Chlorine	Cl	17	35 457	Radon	Rn	86	222
Chromium	Cr	24	52 01	Rhenium	Re	75	186 31
Cobalt	Co	27	58 94	Rhodium	Rh	45	102.91
Columbium	Cb	41	92.91	Rubidium	Rb	37	85 48
Copper	Cu	29	63 57	Ruthenium ...	Ru	44	101.7
Dysprosium	Dy	66	162.46	Samarium	Sm	62	150.43
Erbium ...	Er	68	167 2	Scandium	Sc	21	45 10
Europium	Eu	63	152 0	Selenium	Se	34	78 96
Fluorine	F	9	19 00	Silicon .	Si	14	28.06
Gadolinium	Gd	64	156 9	Silver	Ag	47	107.880
Gallium	Ga	31	69 72	Sodium	Na	11	22.997
Germanium...	Ge	32	72 60	Strontium	Sr	38	87 63
Gold	Au	79	197 2	Sulfur	S	16	32.06
Hafnium ...	Hf	72	178.6	Tantalum	Ta	73	180 88
Helium ...	He	2	4 003	Tellurium	Te	52	127.61
Holmium ...	Ho	67	163.5	Terbium	Tb	65	159.2
Hydrogen	H	1	1 0081	Thallium	Tl	81	204.39
Indium...	In	49	114 76	Thorium	Th	90	232 12
Iodine....	I	53	126 92	Thulium	Tm	69	169.4
Iridium	Ir	77	193.1	Tin ..	Sn	50	118.70
Iron ...	Fe	26	55.84	Titanium	Ti	22	47.90
Krypton	Kr	36	83 7	Tungsten	W	74	183 92
Lanthanum ...	La	57	138 92	Uranium .	U	92	238 07
Lead......	Pb	82	207 21	Vanadium	V	23	50.95
Lithium...	Li	3	6 940	Xenon	Xe	54	131 3
Lutecium...	Lu	71	175.0	Ytterbium	Yb	70	173 04
Magnesium ...	Mg	12	24 32	Yttrium .	Y	39	88 92
Manganese.	Mn	25	54 93	Zinc ..	Zn	30	65.38
Mercury. ...	Hg	80	200 61	Zirconium .	Zr	40	91 22

APPENDIX: TABLE II

PRESSURE CONVERSION FACTORS

1 lb. per sq inch = 52 mm. mercury
1 lb. per sq inch = 70 cm. water
1 inch mercury = 25 mm mercury
1 inch water = 1 87(2) mm. mercury
1 mm. mercury = 1.3 cm. water
1 cm. water = 0.73 mm. mercury
10 mm. mercury = 13.5 cm. water
10 mm. mercury = 0 4 inch mercury
10 mm. mercury = 0 19 lb. per sq inch

APPENDIX: TABLE III
Metric Equivalents
Linear

1 millimeter	= .03937 inch
1 centimeter	= .3937 inch
1 meter	= 39 37 inches
1 inch	= 2.54 centimeters
1 foot	= 30.48 centimeters
1 yard	= 91.44 centimeters

Area

1 square centimeter	= .155 square inch
1 square inch	= 6.4516 square centimeters

Volume

1 cubic centimeter	= .0612 cubic inch
1 cubic inch	= 16.38 cubic centimeters

Fluid Volume

1 cubic centimeter	= 16 23 minims
1 cubic centimeter	= .0338 fluid ounce
1 liter	= 33 815 fluid ounces
1 liter	= 1 0567 quarts
1 fluid ounce	= 29 513 cubic centimeters
1 pint	= 473 167 cubic centimeters
1 quart	= 946 333 cubic centimeters
1 gallon	= 3 785 liters

Weight

1 milligram	= 015132 grams
1 gram	= 15 432 grains
1 kilogram	= 35 274 ounce (adv.)
1 grain	= 64 8 milligrams
1 grain	= 0648 grams
1 ounce (adv.)	= 28 3495 grams

Thermometric Equivalents
C° to F°

Multiply number of centigrade degrees by 9/5 and add 32 to the result

F° to C°

Subtract 32 from the number of Fahrenheit and multiply by 5/9.

Glossary

ABSOLUTE ZERO—(0°A) 273° below 0°C. At this temperature molecular motion is believed to cease.

ABSORPTION—Passage of a substance into the interior of another by solution or penetration.

ACAPNIA—Decrease of carbon dioxide tension in blood below normal value.

ACID—A substance which yields hydrogen ions (H⁺) in solution. Really a substance which yields oxonium (H₃O⁺) in aqueous solution.

ACID ANHYDRIDE—Non-metal oxide which reacts with water to form an acid.

ACID SALT—A salt containing one or more replaceable hydrogen atoms. (NaHCO₃).

ACTION POTENTIAL—Current produced during physiological activity of nerve or other tissue.

ACTIVATE—To induce a state of increased chemical activity.

ACTIVATED CHARCOAL—Charcoal treated to increase its adsorptive power.

ACYCLIC—An open chain compound possessing a ring formation.

ACYL GROUP—An organic radical having the configuration:

$$R\!-\!\overset{\overset{\displaystyle O}{\|}}{C}\!-$$

ADIABATIC PROCESS—A process during which no heat is permitted to enter or escape from the system.

ADSORPTION—A process believed to be physical in nature in which molecules of a gas or liquid condense or adhere, as a film, on the surface of another substance.

AGENT (ANESTHETIC)—Term used by anesthetists to designate an anesthetic drug.

AIRWAY—Pathway for inspired air from lips and nostrils to alveoli.

ALCOHOL—An organic compound, derived from a hydrocarbon, containing one or more hydroxyl (OH) groups.

ALDEHYDE—An organic compound, derived from a hydrocarbon, containing a

$$-\!\overset{\overset{\displaystyle O}{\|}}{C}\!-\!H$$

group.

ALIPHATIC—Open-chain, organic compounds.

ALKALI—A strong, water soluble base.

ALKALOID—Physiologically active substance derived from plants, usually having a complex chemical structure, containing nitrogen, and possessing basic properties.

ALKYL—Radical derived from an aliphatic hydrocarbon, produced by removing one hydrogen from it. A radical cannot exist alone as such.

ALLOTROPY—The ability of certain elements to exist in more than one form, due to a particular arrangement of the atoms or molecules.

ALPHA PARTICLES—Helium atoms which have lost two electrons (produced by radioactive disintegration).

AMALGAM—An alloy composed of mercury and one or more metals.

AMIDE—Ammonia with one hydrogen replaced by an acyl group.

$$R\!-\!\overset{\overset{\displaystyle O}{\|}}{\underset{\underset{\displaystyle NH_2}{|}}{C}}$$

AMINE—Substance produced by replacing one or more hydrogen atoms of ammonia by alkyl or aromatic, alicyclic or heterocylic radicals.

AMORPHOUS—A substance which does not have or does not appear to have a crystalline structure.

AMPHOTERIC SUBSTANCE—A substance which possess radicals which exhibit both acidic and basic properties. COOH-R-NH₂.

ANESTHETIC INDEX—
$$\frac{\text{No. units of anesthetic required for anesthesia}}{\text{No. units of anesthetic required for respiratory failure.}}$$

ANGSTROM UNIT—10⁻⁸ cm., A hundred millionth of a centimeter.

ANHYDRIDE—The residue after the elements of water are abstracted from the acid or base.

ANHYDROUS SUBSTANCE—A substance free from water.

ANION—A negatively charged ion which is attracted to the anode (electrode) during electrolysis.

ANODE—(1) The positive electrode of an electrolytic cell. (2) The electrode where oxidation occurs.

ANTAGONISM—Opposing action of one drug by another.

AROMATIC—Group of compounds derived from benzene and related hydrocarbons.

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ASSOCIATION—The union of simple similar molecules to form complex molecules. Such a union is reversible and remains incomplete.
$X(H_2O)_2 \leftrightarrows (H_2O)_x$.

ATOM—The smallest unit of an element which takes part in the formation of a compound. An atom is a positive nucleus surrounded by electrons.

ATOMIC NUMBER—The net positive charge on the nucleus. This represents the number assigned to the atom in the periodic table.

ATOMIC WEIGHT—The weight of an atom compared to the weight of an oxygen atom taken as 16 000

A-V DIFFERENCE—Difference in volumes per cent between O_2 content of arterial and venous blood.

AVOGADRO'S HYPOTHESIS—Hypothesis stating that at the same temperature and pressure equal volumes of gases contain the same number of molecules.

AVOGADRO'S NUMBER—The number of molecules in a gram-molecule (mole) $6 02 \times 10^{-23}$.

BASE—(1) A hydroxide of a metal which yields hydroxyl ions in solution and neutralizes an acid to form a salt and water. (2) A substance capable of combining with a proton.

BASIC ANHYDRIDE—The oxide of a metal which forms a base when it reacts with water.

BASIC SALT—A salt containing replaceable or hydroxyl groups.

BINARY COMPOUND—A compound whose molecule is composed of two elements.

BOILING POINT—The temperature at which the vapor pressure within a liquid equals atmospheric pressure.

BROWNIAN MOVEMENT—The random agitation of particles of matter of molecular magnitude produced by collision of molecules.

CALORIE—The amount of heat required to raise the temperature of one gram of water from 14°C to 15°C. The large calorie which is used in nutrition equals 1000 calories

CALORIMETER—An apparatus used to measure the amount of heat liberated or absorbed during a chemical or physical reaction

CARBONYL—C=O group, characteristic of ketones but also present in other radicals.

$$\text{O}$$
CARBOXYL —C—OH group, characteristic of organic acids.

CATALYSIS—The change in the rate of a chemical reaction induced by the presence of a substance (called catalyst) which is itself unchanged after the reation is completed.

CATHODE—(1) The negative electrode of an electrolytic cell. (2) The electrode where reduction occurs.

CATION—A positively charged ion which migrates to the cathode in electrolysis.

CHEMICAL EQUILIBRIUM—The state of balance between two chemical reactions proceeding at equal rates but in opposite direction, each undoing the work of the other.

COMPLEX ION—Ions produced by the union of a number of simple ions, or by the union of a simple ion with molecules.

COMPLEX SALT—A salt which contains complex ions.

COMPOUND SUBSTANCE—A substance which can be decomposed into recognized elements

CONJUGATION—Addition of a new group by a biochemical mechanism to a chemical substance which changes its physiological activity.

COVALENT MOLECULE—A molecule in which the bond between two atoms is a shared electron pair, such as $H:Cl$, $H:H$, $Cl:Cl$.

"CRACKING"—A process in which hydrocarbons of high molecular weight are broken down into smaller molecules by the aid of heat and pressure.

CRITICAL PRESSURE—The minimum pressure required to liquefy a gas at the critical temperature.

CRITICAL TEMPERATURE—The temperature above which a gas cannot be liquefied regardless of the pressure used.

CRYSTALLOID—A material which when dispersed in a dispersion medium forms a true solution.

CYCLIC—Closed-chain chemical compound.

DEGRADATION—A disintegration of a chain of carbon atoms in a stepwise manner

DENSITY—Mass per unit volume, e g , grams per cubic centimeter

DEPRESSION—Decrease of power of cells to function

DERIVATIVE—The resultant of a chemical reaction

DETONATOR—Flame, fuse, shock or other agent which causes an explosive mixture to explode.

DEUTERIUM—The isotope of hydrogen having a mass of 2.

DEXTROROTATORY—Rotating a plane of polarized light to the right

DIBASIC ACID—Acid with two replaceable hydrogen atoms in its molecule.

DIFFUSION—(1) Passage of molecules through membranes (such as in alveoli), (2) The spreading apart of molecules of gases or fluids.

DISTILLATE—The vapor which condenses and is caught in the receiver of a distillation apparatus.

DISSOCIATION—Reversible decomposition of complex molecules into simpler molecules

DISSOLVE—The dispersion of one material into another so that an apparently homogeneous mixture forms. There may or may not be chemical alteration

DOUBLE SALT—A salt in which two atoms of a metal are combined with one acid radical or one atom of a metal is combined with two acids.

DYNE—The force necessary to impart to a mass of one gram an acceleration of one centimeter per second per second.

EFFLORESCENT SUBSTANCE—A substance which loses water of crystallization when exposed to air, e.g., $Na_2CO_3 \cdot 10H_2O \rightarrow Na_2CO_3H_2O$.

ELECTROCHEMICAL SERIES—A list of metals arranged in the order of decreasing tendency to be oxidized, or to react with acids to liberate hydrogen.

ELECTRON—The unit of negative electricity which possess a mass equivalent to $\dfrac{1}{1845}$ of the hydrogen atom.

ELEMENTARY SUBSTANCE—One of a small group of substances of nearly complete stability whose chemical properties give each of them a definite place in the Periodic Table.

EMULSION—A dispersion in which the dispersed phase is a liquid and dispersion medium is a liquid.

ENDOGENOUS—Arising from sources within the organism.

ENDOTHERMIC—Reaction absorbing heat.

END POINT—The completion of a reaction usually evident by the first perceptible alteration of the color of an added indicator.

ENZYME—A substance elaborated by living cells which possess catalytic properties.

EPOXY—A group which has the structure

$$\begin{array}{c} O \\ / \backslash \\ -C-C- \\ | \quad | \end{array}$$

EQUILIBRIUM—A state of balance between two opposing forces or processes.

EXOTHERMIC—Reaction accompanied by the evolution of heat.

EXPLOSIVE MIXTURE—Mixture capable of extremely rapid combustion.

FERMENTATION—A chemical reaction accomplished by living cells to liberate energy anaerobically aided by enzymes.

FIXATION OF NITROGEN—The conversion of atmospheric nitrogen into nitrogen containing compounds such as ammonia, nitrates etc.

FLASH POINT—Lowest temperature at which vapors of a liquid may be ignited by a flame.

FLUORESCENCE—A process in which light is absorbed and is instantaneously re-emitted with altered frequency.

FOAM—A dispersion in which the dispersed phase is a gas and the dispersion medium is a liquid.

FRACTIONAL DISTILLATION—The process by which two or more liquids of different boiling points

are separated by distillation and each fraction, as it forms, is collected in separate containers.

GRAM ATOM—Atomic weight of an element expressed in grams.

GRAM MOLECULE—The molecular weight of an element or compound expressed in grams.

HALIDE—A substance composed of a radical and one or more halogen atoms.

HALOGENS—The elements fluorine, chlorine, bromine and iodine.

HEAT OF DISSOCIATION—The heat (expressed in calories) expended in the dissociation of one mole of a substance into specified products.

HEAT OF FORMATION—The heat in calories which is absorbed or liberated during the reaction in which a mole of a compound forms from the necessary elements.

HEAT OF VAPORIZATION—Heat in calories required to change a unit weight of liquid to the vapor state at a given temperature.

HEAVY WATER—Water which contains deuterium in a place of the ordinary hydrogen atom.

HETEROCYCLIC—Cyclic structure containing other elements beside carbon in the ring.

HUMIDITY (ABSOLUTE)—The amount of water vapor present per unit volume of gas or air when saturated.

HUMIDITY (RELATIVE)—The actual amount of water vapor present in the air or a gas divided by the amount necessary for saturation at the same temperature and pressure expressed in per cent.

HYDROGENATION—Process of adding hydrogen (to an unsaturated compound).

HYDRATE—A crystalline substance containing a definite proportion of chemically combined water.

HYDROLYSIS—Reaction between the ions of a salt and those of water to form an acid and base, one or both of which is only slightly dissociated.

HYDROUS—Combined with an indefinite or variable amount of water.

HYGROSCOPIC—A substance which absorbs moisture from the atmosphere.

HYPERBARIC—Specific gravity of a solution which is greater than that of spinal fluid.

HYPOBARIC—Specific gravity of a solution less than that of spinal fluid.

INDICATOR—A substance capable of undergoing a color change at a definite hydrogen ion (or other specific ion) concentration.

INDUCTION—Period from start of anesthesia to attainment of third stage.

INERT ELEMENT—An element located in the zero group of the Periodic Table.

INTERFACE—The surface which separates two phases.

ION—An atom or group of atoms bearing a positive or negative charge.

IONIZATION—The formation of ions by reaction with a solvent.

IONIZATION CONSTANT—The product of the concentration of the ions divided by the concentration of the unionized molecules of an electrolyte.

ISOELECTRIC POINT—The pH at which an emulsoid colloid exhibits a minimum of swelling and may be nearly precipitated.

ISO—A prefix placed before the name of an aliphatic compound indicating branching of the chain.

ISOMERISM—State in which two compounds have the same composition but different molecular structures.

ISOMERS—Molecules composed of the same number and types of atoms but which are arranged differently within the molecule.

ISOTHERMAL PROCESS—A process occurring without the admission or escape of heat.

ISOTOPES—Atoms which possess the same atomic number but slightly different atomic weights but almost identical chemical properties.

LATENT HEAT—The quantity of heat expressed in calories which is absorbed or liberated when a mole of substance changes from one state to another at a fixed temperature, e.g. conversion of 18g. of ice to water at 0°C. requires 1440 calories of heat or 80 calories per gram.

LATENT HEAT OF VAPORIZATION—The amount of heat in calories required to change a unit mass of a substance existing in a liquid form at a given temperature into a vapor without change of temperature. The heat of vaporization for water at 100°C. is approximately 536 calories per gram.

LAW, LE CHATELIER'S—If external factors such as temperature and pressure disturb a system in equilibrium adjustment occurs in such a way that the effect of the disturbing factors is reduced to a minimum

LEVOROTATORY—Rotating the plane of polarized light to left.

LIPOPHILIC—Showing marked attaction or solubility in lipoids.

MACERATE—The process of softening a solid by steeping it in a liquid.

MARGIN OF SAFETY—Margin between the therapeutic dose and lethal dose.

MASS ACTION, LAW OF—The speed of a chemical change is proportional to the concentration of the reacting substances.

MELTING OR FREEZING POINT—The temperature at which the solid and liquid phases of any pure substance are in equilibrium.

MERCAPTAN—An alcohol in which sulphur replaces oxygen in the hydroxyl group to form an (SH) group.

METAMER—A chemical compound which resembles

another in properties but differs from it in structure and composition.

MOLAL—A solution in which one gram molecular weight of solute is dissolved in one thousand grams of solvent.

MOLAR SOLUTION—A solution which contains one mole of solute per liter of solution.

MOLE—The molecular weight of a substance expressed in grams.

MOLECULAR WEIGHT—The sum of the atomic weights of all the atoms in a molecule.

MONOBASIC ACID—An acid having one replaceable hydrogen atom in its molecule.

N—Refers to Nitrogen—a radical is attached to nitrogen in a compound. N-methyl means a methyl group attached to the nitrogen atom.

n-Normal—refers to straight-chain compound. n-propane.

NASCENT—The state of an element at the instant it is liberated from a compound.

NEUTRALIZATION—Union of hydrogen and hydroxyl ions to form undissociated molecules of water.

NORMAL SOLUTION—A solution containing an active reagent which may replace unite with, liberate or causes to react one gram of hydrogen per liter.

OCCLUSION—The process by which large volumes of gases are absorbed by solids.

OXIDATION—(1) The combination of oxygen with other elements to form oxides (2) The process in which an element gains electrons.

OXIDATION POTENTIAL—The measure of the tendency of a substance to be oxidized to some specified other substance, under specified conditions.

OXONIUM ION—The ion H_3O^+, formed by direct union of a proton with water. The oxonium ion forms when an acid dissolves in water. The old concept was that hydrogen (H⁺) ion was formed.

OXYGEN CAPACITY (Vol. %)—Maximum amount of oxygen a given volume of blood absorbs when equilibrated with an excess of oxygen expressed in cc. per 100 cc.

OXYGEN CONTENT (Vol. %)—Oxygen in volumes per cent present in blood at a given moment.

OXYGEN SATURATION—Oxygen content divided by oxygen capacity expressed in volumes per cent

PARALYSIS—Cessation of cell function.

PERIODIC TABLE—A table of the elements, arranged in rows and columns. The different columns represent different groups of chemically similar elements.

pH—Concentration of hydrogen ions expressed as the log of the reciprocal of the concentration

PHASE—A homogenous portion of matter which is distinct in composition and properties from other phases in contact with it.

PLANE—Level or "stratum" of third stage anesthesia.

POLYMER—A new compound formed by the combination of several molecules of a substance. The compound has a percentage composition the same as the initial compounds but the molecular weight is a multiple of the initial compound.

POLYMORPHISM—The ability of a substance to exist in two or more crystalline forms.

POSITRON—A unit charge of positive electricity which has approximately the same mass as an electron.

POTENTIATION—Addition of one drug to another to increase its action.

PRECIPITATE—An insoluble solid substance which forms from chemical reactions between solutions.

PRESSURE—*The force exerted against a unit area* usually expressed in dynes or grams per square centimeter, or in pounds per square inch.

PROTON—A positively charged hydrogen atom, H⁺, which is identical with the hydrogen nucleus

QUALITATIVE TEST—A test which attempts to identify a material or the ingredients of a mixture.

QUANTITATIVE TEST—A test used to determine the actual amount of a given substance in a mixture or compound.

RACEMIC—A mixture of equal portions of a dextro and a levo compound. There is no rotation of the plane of polarized light.

RADICAL—A group of atoms capable of acting as single element in chemical reactions.

RADIOACTIVE—The continuous discharge of invisible rays, which affect the photographic plate, the electroscope, or produce a visible fog in moist air.

REACTIVITY—Possessing the tendency toward entering into a specified chemical reaction.

RECTIFY—Purification of a substance by fractional distillation.

REDUCTION—Removal of oxygen; addition of hydrogen, gain of *electrons*.

REDUCING AGENT—(1) A substance capable of removing oxygen from another substance. (2) A substance which contains an atom which donates one or more electrons

REPLACEMENT SERIES—An arrangement in which the metals are listed in order of their decreasing chemical activity.

REVERSIBLE REACTION—A reaction which under proper conditions can progress in both directions at one time.

SAPONIFICATION—The hydrolysis of fats and oils by alkalies and water to form soaps and alcohols.

SATURATED SOLUTION—A solution in which an equilibrium exists between undissolved solute and dissolved solute.

SATURATED VAPOR—This condition is present when *the space above a liquid contains all the vapor it can acquire and hold at the given temperature and which is in equilibrium with the liquid.*

SOLUBILITY PRODUCT CONSTANT—The product of the concentrations of ions in a saturated solution of a slightly soluble salt at a given temperature.

SOLUTE—The substance which dissolves in a solvent.

SOLVENT—The constituent of a solution which does the dissolving and is present in greater amounts.

SPECIFIC GRAVITY (GASES)—The ratio of the weight of one liter of gas compared to the weight of one liter of air.

SPECIFIC GRAVITY (SOLID OR LIQUID)—*The ratio of* the weight of a unit volume of a substance to the weight of an equivalent volume of water.

SPECIFIC HEAT—The heat required to raise the temperature of one gram of a substance from 14–15°C.

SPECTRUM—The separation of light into its component parts by the aid of a prism or grating.

STABLE—A term applied to a substance which has no tendency to decompose spontaneously.

STABILITY (as applied to compounds)—The property of being able to resist being decomposed or chemically altered.

STANDARD CONDITIONS—*0°C. and 1 atmosphere* pressure (760 mm. Hg).

STANDARD ATMOSPHERIC PRESSURE—The pressure caused by the weight of the atmosphere at sea-level. It is a pressure of 1033 grams per square centimeter or 14.9 pounds per square inch. It elevates mercury in a barometer to a height of 760 mm

STIMULATION—Increased functioning of protoplasm induced by some extra cellular substance or agent.

STRONG ACID—*An acid which is completely ionized* in aqueous solution.

SUBLIMATION—The transformation of a solid to a vapor without its passing through the liquid state.

SUPERCOOLING—The cooling of a liquid below its freezing point, without freezing occurring.

SURFACE TENSION—Contraction force of a surface, usually expressed in dynes per square centimeter.

SUSPENSION—A dispersion in which the dispersed *phase is composed of a solid.*

SYNERESIS—Spontaneous shrinkage of a gel, accompanied by slow separation of liquid.

SYNERGISM—Production of an effect by two drugs possessing similar action acting together which is greater than the sum of each if they act alone.

TENSION—Pressure of a gas.

TERNARY COMPOUND—A compound whose molecule is composed of three elements.

THIO—Prefix indicating sulphur-containing compound.

TINCTURE—Alcoholic solution of a compound.

TITRATION—The measurement of the volume of liquid needed to complete a given chemical reaction.

TRIBASIC ACID—An acid containing three replaceable hydrogen atoms in each molecule.

VALENCE (1) The number of atoms of hydrogen (or equivalent elements) which combine with, or are replaced by the atom in question. (2) Polar valence is the excess of positive or negative changes on an atom or radical. (3) Non-polar valence is the number referring to electron pairs shared with other atoms.

VAPOR DENSITY—The ratio of the weight of a gas or vapor to the weight of an equal volume of hydrogen measured under the same conditions of temperature and pressure

VAPOR PRESSURE—The partial pressure exerted by a vapor.

VISCOSITY—Resistance to flow of fluids due to the internal friction of the liquid.

VOLUMES PER CENT—(Blood) cc. of gas liberated from 100 cc. of liquid.

WATER OF HYDRATION—The water contained in a hydrate.

WEAK ACID—An acid which is only slightly ionized in aqueous solution.

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Chapter 31

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